BENZOTRIAZOLE-PHOSPHORUS REAGENTS IN ORGANIC SYNTHESIS

BY

JINLONG JIANG

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1993

To my wife Qingmei and daughter Eileen

ACKNOWLEDGMENTS

I am deeply indebted to Professor Alan R. Katritzky for his invaluable guidance, trust and help during these years. It has been a rewarding experience and a pleasure to work with him.

I would like to express my gratitude to Dr. William Jones, Dr. Kirk Schanze, Dr. John Eyler and Dr. Heinrich Eicchorn for their help, suggestions and time as my supervising committee members.

I want to give my thanks to Dr. Laszlo Urodgi, Dr. Philip Harris, Dr. John Greenhill and Dr. Weigiang Fan for their help and cooperation during these years. Special thanks go to Dr. John Greenhill and Ms. Linghong Xie for their valuable help in reading and correcting this manuscript.

I want to thank "my roommate" (Dr. V. Motikov); the time we worked together was always memorable. And to thank the people in the ARK research group for their companionship, friendship and help during these years.

I am indebted to my family for all their love and encouragement, especially to my wife, Qingmei, for her support, help, understanding, and for her struggles with CHEMTEXT over this manuscript.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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By
Jinlong Jiang
May, 1993

Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

The novel 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (betmip) was prepared from benzotriazol-1-ylmethyl azide and triphenylphosphine. Betmip reacted readily with carbanions, lithium amides, primary amines, thiol anions, diethyl phosphite anion and methylenetriphenylphosphorane to give diverse α-substituted N-methyliminophosphoranes, most of which are new. The resulting iminophosphoranes were transformed, without isolation, into primary amines, carbodiimides, imines, isothiocyanates, aziridines, secondary amines, 1,4,5-trisubstituted imidazoles, α-(arylideneamino)alkylamines, N-(alkylthiomethyl)-benzalimines, N-(alkylthiomethyl)-N′-alkylcarbodiimides, N-(alkylthiomethyl)--N′-alkylureas, N-(alkylthiomethyl)amides, isoquinoline, 2-azabutadienes, 1,8-diphenyl-4-azaoctatetrene, 2-(*3H*)-benzazepine and 2,3-disubstituted pyrroles. Many of the prepared compounds are novel.

Condensation of an aldehyde, an oxime and benzotriazole gave an O-(1-benzotriazolylalkyl)oxime which underwent an addition-rearrangement on treatment with an organolithium reagent. This reaction provides a novel non-oxidative method for the transformation of aldehydes into amides which has afforded several new N-monosubstituted amides with crowded structures. Grignard reactions of the O-(1-benzotriazolylalkyl)oximes gave alcohols as the major products.

CHAPTER I
AN INTRODUCTION TO BETMIP

Benzotriazole is a benzo derivative of *1H*-1,2,3-triazole in which the triazole moiety has its two carbons shared with the benzene ring. One important feature of benzotriazole is the strong electron-withdrawing nature of the nitrogen-nitrogen double bond which is reflected in the high acidity of benzotriazole. This acidity gives benzotriazole one of its very important characteristics, *i.e.* the benzotriazole anion is a good leaving group. It may be used in place of a halogen substituent in many reactions. The benzotriazole group has the advantage, however, that the derivatives are frequently much more stable than their chloro or bromo analogues. For example, α-benzotriazolylalkyl ethers are stable, easily prepared compounds, whereas the corresponding α-chloroalkyl analogues are highly reactive and, in some cases, physiologically dangerous. In recent years, benzotriazole has been extensively used as a synthetic auxiliary in this research group and many types of organic compounds, *e.g.* various aliphatic and aromatic amines, hydroxylamines, hydrazines, amides, aminoacids, ethers, esters *etc.* have been synthesized.

This project is to investigate the reactivity and applications of a new reagent, betmip, which combines the good leaving group nature of benzotriazole and a ready reaction with carbonyl compound characteristics of the N=P group. Betmip (Fig.1.1) is an abbreviation of 1-(triphenylphosphoroylideneaminomethyl)benzotriazole. The term betmip consists of "bet," "m," "i" and "p" which, respectively, represent "benzotriazole," "methylene," "imino" and "phosphorane."

The synthesis of betmip consists of four simple steps starting from the inexpensive starting materials, aqueous formaldehyde and benzotriazole. Each step

gives a nice solid product in a quantitative yield (Scheme 1.1).

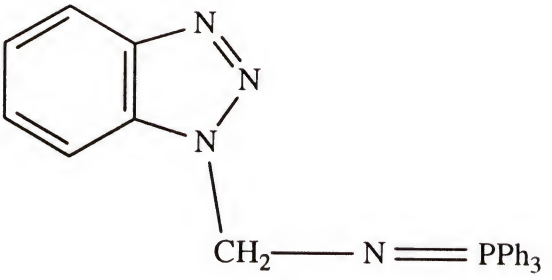
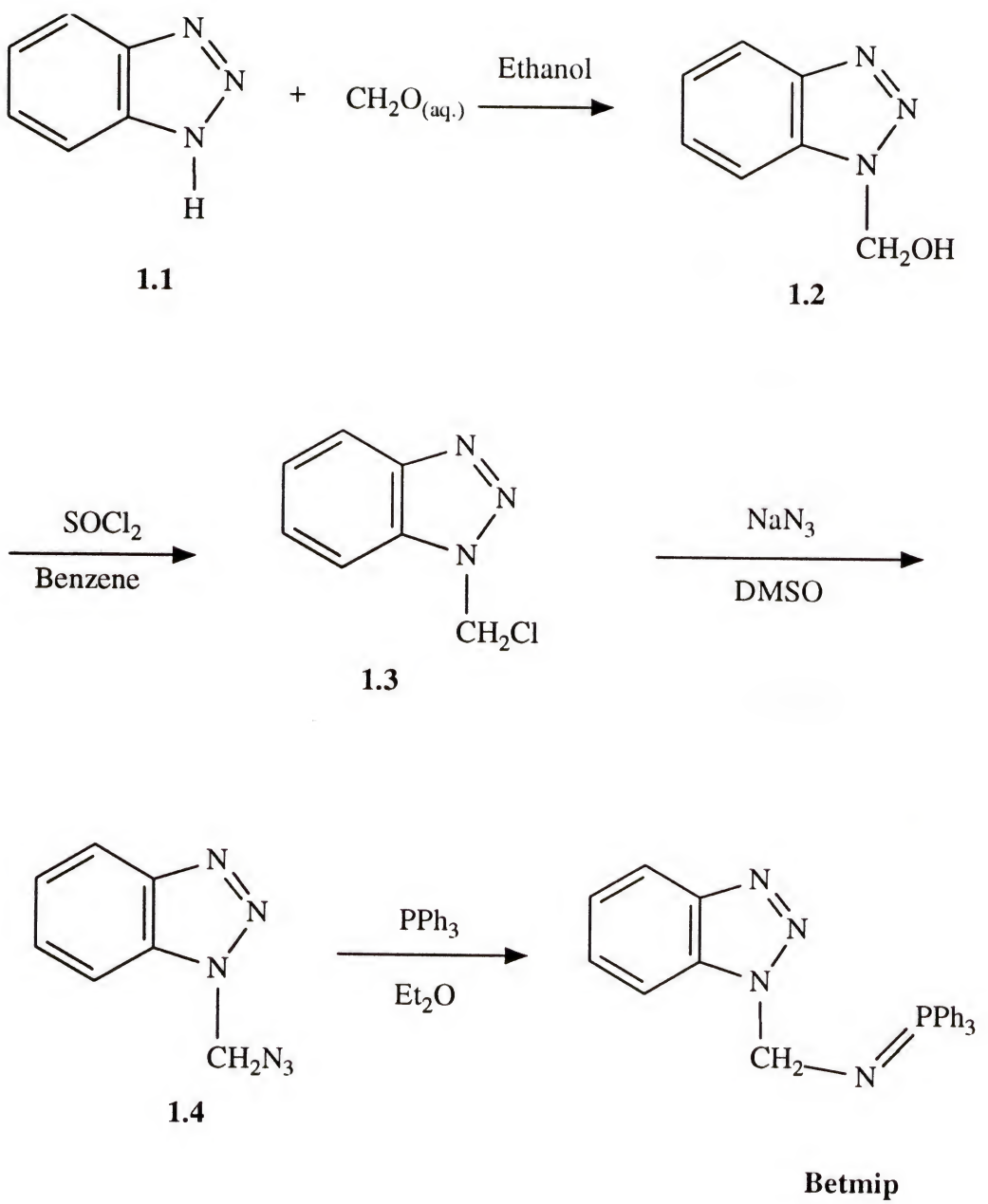


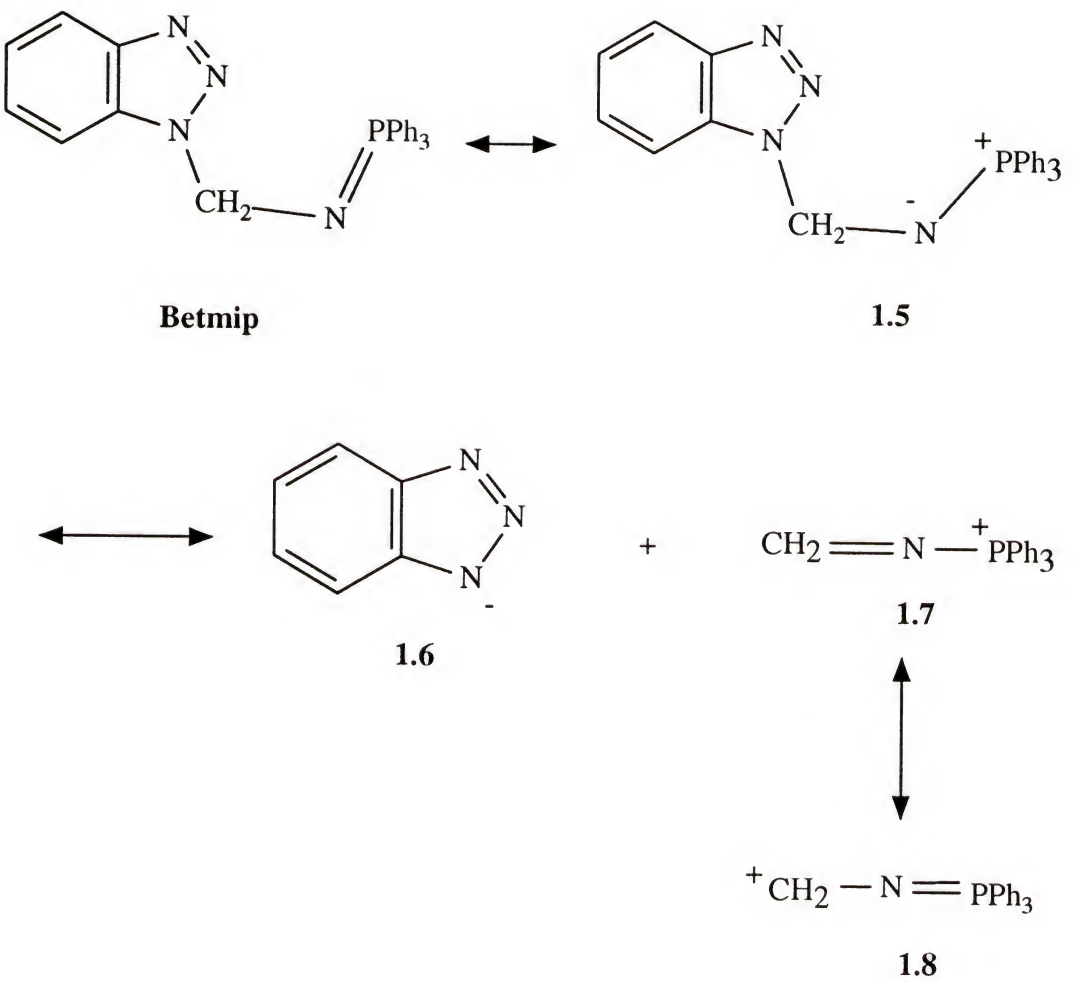
Fig. 1.1 Betmip

The main feature of betmip is the existence of both electrophilic and nucleophilic centers which are, respectively, situated on the methylene carbon and the nitrogen atom of the $CH_2N=P$ unit. The nucleophilic substitution on the methylene carbon leads to displacement of benzotriazole with formation of a nucleophile-carbon bond. Compared with the Mannich type of the benzotriazole derivatives, benzotriazole in betmip is more easily displaced by nucleophiles; for example, the substitution by a carbanion could be carried out even at 0°C. The easy displacement of benzotriazole in betmip can be rationalized by the assistance of the formal negative charge on the nitrogen atom of the N=P group which pushes the benzotriazole to leave or makes the right side of the resonance equation more favorable, Scheme 1.2. Thus, betmip is equivalent to **1.7**, and the mechanism of the displacement of the benzotriazole group is actually the addition of a nucleophile to **1.7**, which is resonant with **1.8**.

The N=P group in betmip possesses characteristics similar to Wittig reagents which can undergo an addition to a carbonyl group, then an elimination of triphenylphosphine oxide to give a C=N bond. However, the N=P bond in betmip is



Scheme 1.1 Synthesis of Betmip

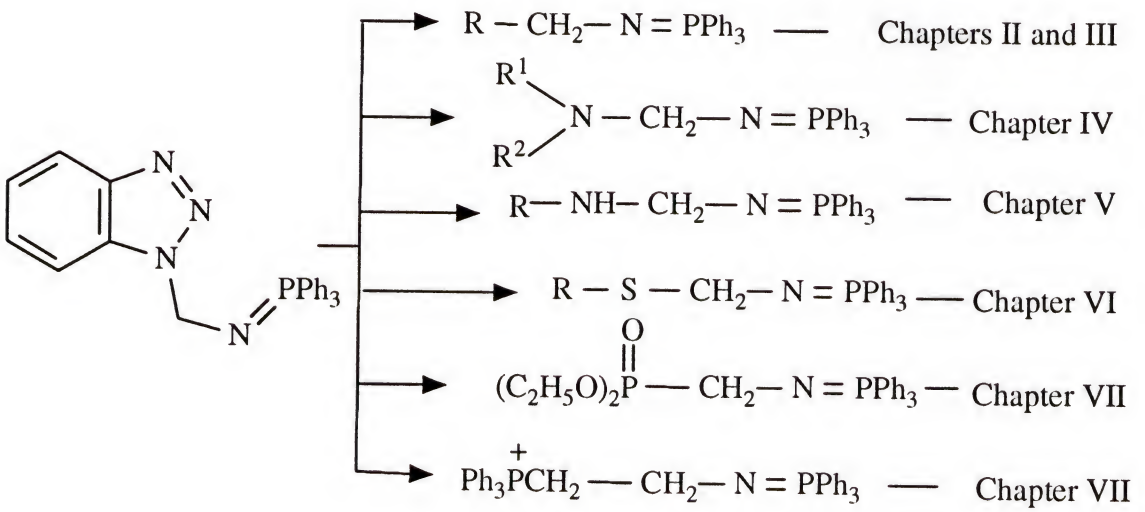


Scheme 1.2

much less reactive than other iminophosphoranes due to the electron-withdrawing characteristics of benzotriazole. The lower reactivity was observed in the reaction with an epoxide. Betmip did not react with styrene epoxide in refluxing THF. However, after initial Grignard reaction to replace benzotriazole, the resulting iminophosphoranes were readily transformed into aziridines (see Chapter III).

In summary, the interaction between benzotriazole and the N=P group in betmip leads to an enhanced reactivity of the electrophilic center and a decreased reactivity of the N=P bond. The higher reactivity of the N=P bond can be released after the displacement of benzotriazole by a nucleophile, which is usually less electron-withdrawing than benzotriazole. This interaction gives betmip good stability which makes its preparation convenient and allows prolonged storage.

The applications of betmip in organic synthesis are *via* several iminophosphorane intermediates (α-substituted N-methyliminophosphoranes, Scheme 1.3) from the displacement of benzotriazole by a variety of nucleophiles. The resulting iminophosphoranes can then undergo reactions with diverse electrophiles.



Scheme 1.3

Chapter II and Chapter III are concerned with the reactions of iminophosphoranes formed *in situ* from Grignard reagents. In these cases, betmip acts a novel $^{+}CH_2NH_2$ synthon and the first $^{+}CH_2N=$ synthon. Chapter IV covers the synthesis of

α-(arylideneamino)alkylamines from secondary amines and aldehydes. Chapter V describes the synthesis of 1,4,5-trisubstituted imidazoles derived from the reactions of betmip with primary amines and α-diketones. Chapter VI discusses the synthesis of formaldehyde N,S-acetals. Finally, Chapter VII is concerned with the reactions of betmip with diethyl phosphite anion and methylenetriphenylphosphorane followed by treatment with butyllithium to give 1,2- and 1,3-monoazabisylides, respectively.

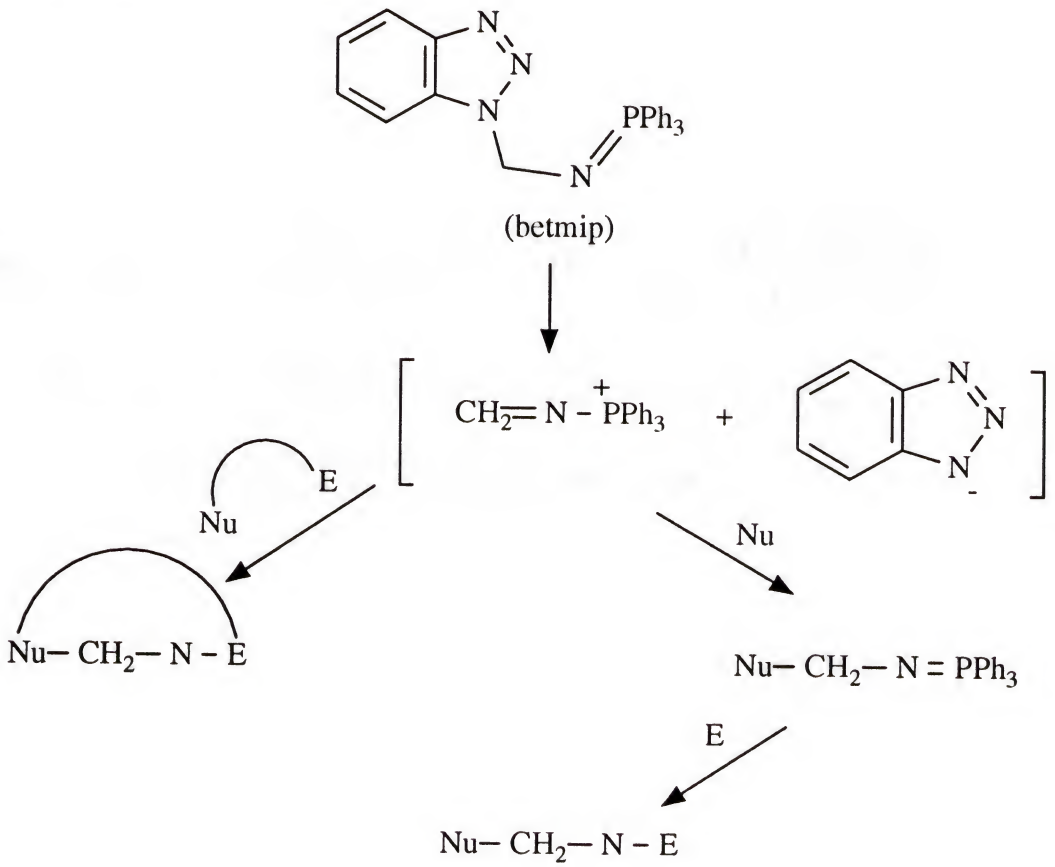
1.1 Procedure for the Preparation of Betmip

Triphenylphosphine (18.0 g, 68.6 mmol) in diethyl ether (50 ml) was added dropwise to a stirring solution of benzotriazol-1-ylmethyl azide [87JCS(P1)781] (11.8 g, 68 mmol) in diethyl ether (100 ml). After stirring for 1 hr at room temperature, the precipitate was collected as a colorless solid product (26 g, 95%, m.p. 99-101°C). ^{1}H NMR (run on Varian VXR-300 instrument, FT mode, in $CDCl_3$): ^{1}H NMR (δ/TMS) 6.11 (2 H, d, J = 30 Hz, CH_2), 7.24-7.92 (19 H, m, aromatic); ^{13}C NMR (δ/$CDCl_3$, 77.00) 146.2, 132.7, 126.2, 123.2, 119.3, 111.6 (benzotriazole), 132.5, 132.4, 131.7, 131.6, 130.4, 129.1, 128.5, 128.4 (phenyl), 62.45 and 62.40 (CH_2). Elemental analysis for $C_{25}H_{21}N_4P$ calculated: C: 73.52, H: 5.18, N: 13.72; found C: 73.30, H: 5.16, N:13.60.

1.2 Aim of the Work

Vinyltriphenylphosphonium bromide (CH_2=$CHP^+Ph_3Br^-$) as a valuable ylide precursor has been widely used in organic synthesis. The analogous CH_2=$NP^+Ph_3X^-$ (X = halogen), however, has not been reported in the literature. The goal of this project

was to develop a reagent of the $CH_2=NP^+Ph_3$ type or its equivalent to provide a good general method for the synthesis of nitrogen-containing compounds or heterocycles, Scheme 1.4.

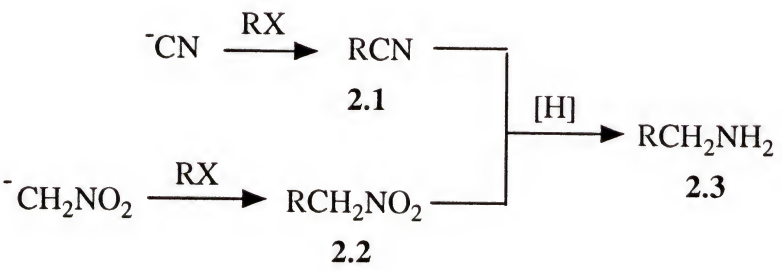


Scheme 1.4

CHAPTER II
BETMIP, A NOVEL SYNTHON OF $^{+}CH_2NH_2$: APPLICATION TO ONE-POT SYNTHESIS OF PRIMARY AMINES

2.1 Introduction

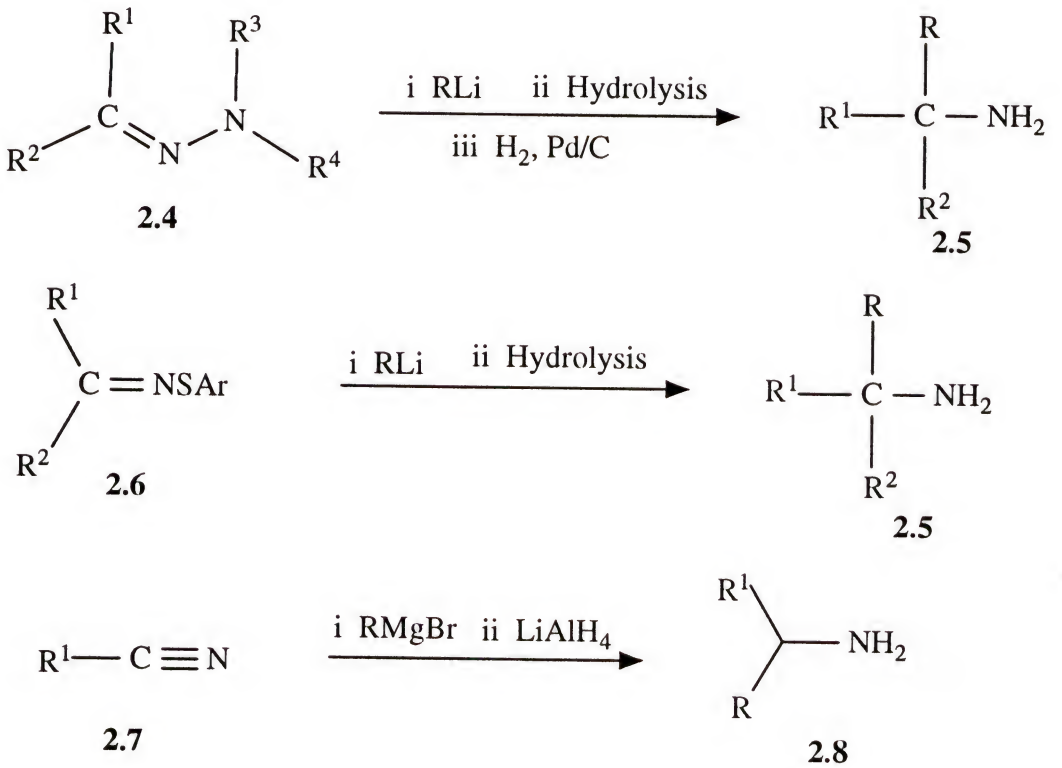
The preparation of primary amines **2.3** has been accomplished by the connection of a H_2NCH_2 fragment to a functionalized carbon atom, by using both nucleophilic and electrophilic aminomethylation reactions. The substitution of a leaving group (often a halogen atom) by cyanide [79MI9] or by nitromethide anion [85SC71]] followed by the reduction of the resulting nitriles **2.1** or nitro compounds **2.2** represents classical, and widely used, examples of the nucleophilic version, Scheme 2.1.



Scheme 2.1

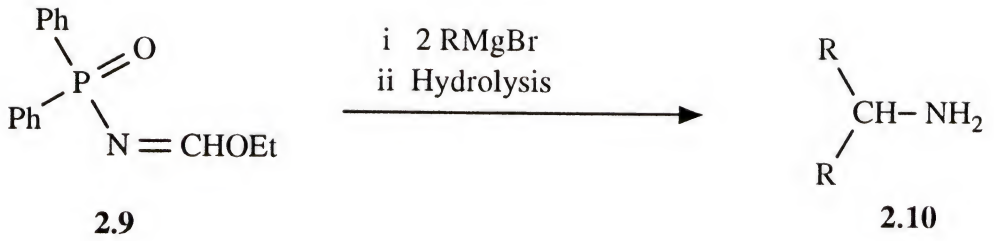
However, the similar conversion of a carbanion (i.e. an organometallic reagent) to one-carbon higher homologous primary amines has attracted much less attention. Addition of organometallic reagents to the carbon-nitrogen double or triple bonds (hydrazones **2.4** [79MI15], alkylidenearenesulfenamides **2.6** [77JOC398], or nitriles

2.7 [73TL1057]) followed by hydrogenation (for hydrazones **2.4** and nitriles **2.7**) or hydrolysis (for alkylidenearenesulfenamides **2.6**) do result in primary amines, but always with α-branched carbon skeletons, Scheme 2.2.



Scheme 2.2

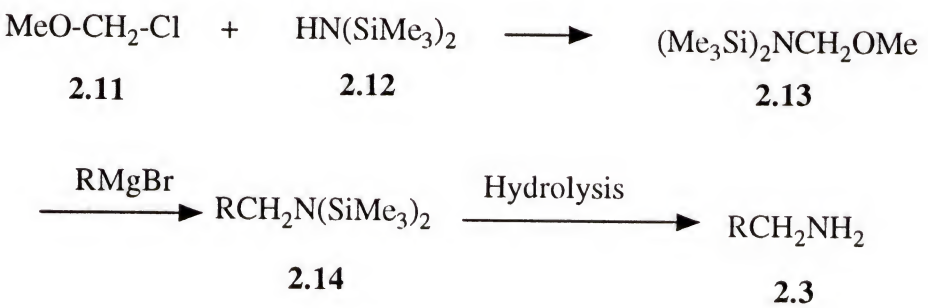
Similarly, the addition of Grignard reagents to the C=N double bond of ethyl N-diphenylphosphinylformimidate, $Ph_2P(O)N{=}CHOEt$ (**2.9**) [79S691], and simultaneous substitution of the ethoxy group gives, after deprotection, secondary alkyl primary amines, R_2CHNH_2, in high yields, Scheme 2.3.



2.9 **2.10**

Scheme 2.3

Recently, Japanese [84CC794] and German [84AG(E)53] groups reported, simultaneously but independently, on N,N-bis(trimethylsilyl)methoxymethylamine (**2.13**), a synthon equivalent to $^{+}CH_2NH_2$, and on the application of this reagent to the synthesis of primary amines **2.3** by reactions with organometallic reagents, Scheme 2.4.



2.11 **2.12** **2.13** **2.14** **2.3**

Scheme 2.4

However, the method has some drawbacks. The reagent requires tedious preparation from hexamethyldisilane through lithium or sodium bis(trimethylsilyl)amide [61CB1540], reaction with the expensive and highly carcinogenic chloromethyl methyl ether **2.11**, and the chemical yields of the protected amines **2.13** are only moderate in some cases. Thus, a versatile, convenient and high-yielding preparative method for the conversion of carbanions to one-carbon higher homologous

primary amines is desirable.

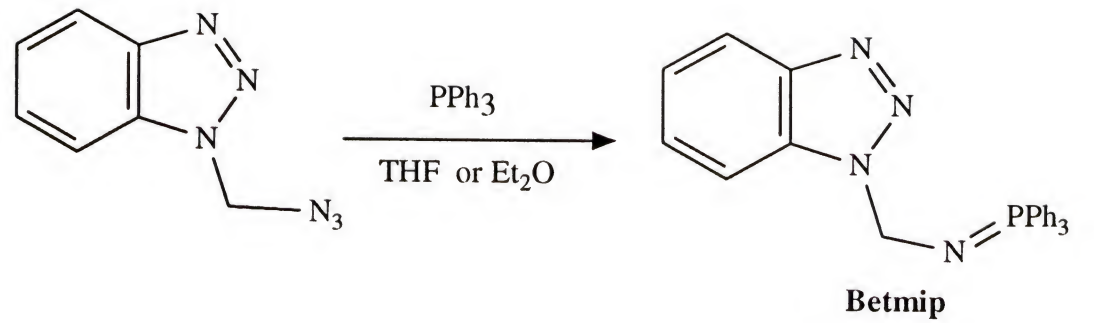
We now report a new reagent 1-(triphenylphosphoroylideneaminomethyl)-benzotriazole, a more convenient $^{+}CH_2NH_2$ synthon, and its application to the one-pot synthesis of primary amines of the type RCH_2NH_2, Scheme 2.5.

2.2 Results and Discussion

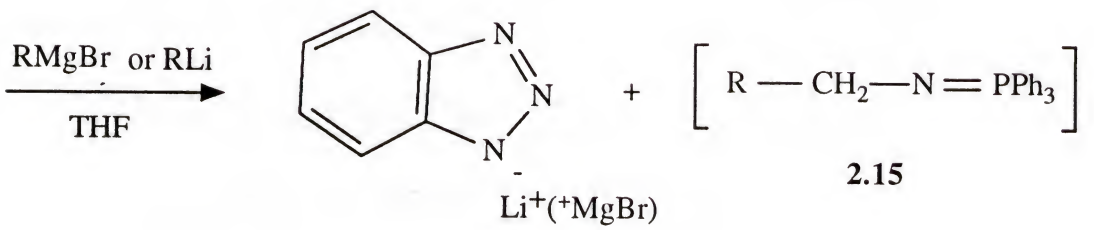
The reparation of betmip was conveniently accomplished by the Staudinger reaction as mentioned earlier. Although betmip is not soluble in diethyl ether, the reaction could be carried out in THF which is the best reaction solvent.

The benzotriazole moiety of betmip can be replaced by alkyl or aryl groups with organometallic (Grignard or lithium) reagents, similar to other 1-(benzotriazolylalkyl)amine derivatives (Mannich base) [87JCS(P1)805] [89S31]. The resulting iminophosphoranes **2.15**, without isolation, undergo spontaneous hydrolysis [83TL763] [85BSF815] during the basic work-up procedure to give primary amines **2.3** which are conveniently converted into hydrochlorides **2.17** for isolation.

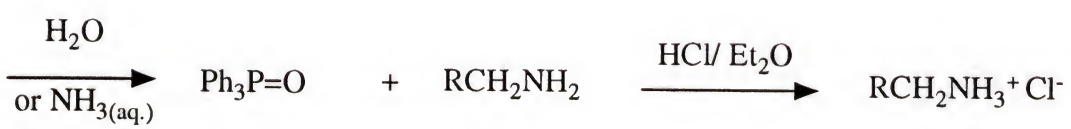
The side product, the lithium salt of benzotriazole or benzotriazolyl magnesium halide, was removed with the basic aqueous layer in the extraction step, while the triphenylphosphine oxide (**2.16**) remained in the ethereal mother liquor during the isolation of the hydrochloride **2.17**. The examples in Table 2.1 demonstrate the versatility of the procedure: alkyl, cycloalkyl, aralkyl, aryl and heteroaryl Grignard reagents and phenylethynyllithium gave equally high yields. The yields are significantly higher than those obtained in comparable cases by use of N,N-bis(trimethylsilyl)methoxylmethylamine: e.g. 77% for cyclohexyl-



Betmip



2.15



2.16 **2.3** **2.17**

Compd	**2.17a**	**2.17b**	**2.17c**	**2.17d**	**2.17e**	**2.17f**	**2.17g**
R	$C_6H_5CH_2$,	C_6H_5,	n-$C_{12}H_{25}$,	$C_6H_5C{\equiv}C$	c-C_6H_{11},	2-Thienyl,	1-Naphthyl

Scheme 2.5

Table 2.1 Preparation of Primary Amine Hydrochlorides **2.17**

Compd	Yield [b] (%)	R	X[a]	Method	m.p.(°C)	Lit. m.p. (°C)
2.17a	67	$C_6H_5CH_2$	MgCl	A	220-221[c]	216-217 [29MI(12)1096]
2.17b	82	C_6H_5	MgBr	B	255-256[d]	253 [29MI(12)445]
2.17c	87	n-$C_{12}H_{25}$	MgBr	A	150(dec.)[d]	160(dec.) [22MI(4)201]
2.17d	86	$C_6H_5C{\equiv}C$	Li	A	222-223[c]	216-216 [76JOC2571]
2.17e	77	c-C_6H_{11}	MgBr	A	254-257[c]	254 [29MI(12)12]
2.17f	84	2-Thienyl	MgBr	A	199-200[c]	193-194 [34MI(18)7097]
2.17g	93	1-Naphthyl	MgBr	A	264-266[d]	262-264 [29MI(12)740]

a All organometallic reagents were prepared in dry diethyl ether by standard methods.

b Yield of the crude product before recrystallization; all crude products gave clear ^1H and ^{13}C NMR spectra.

c Melting point obtained after recrystallization from an ethanol-acetone mixture

d Melting point of the crude product

methylamine-HCl, and 86% for phenylpropargylamine-HCl, vs 52% and 61% [84CC794], respectively. Moreover, betmip and iminophosphoranes **2.15** need not necessarily be isolated, as demonstrated by the one-pot preparation of benzylamine hydrochloride from benzotriazol-1-ylmethyl azide (Procedure B).

Table 2.2 Comparison of the Present Yields of **2.17** with Those of $RCH_2N(SiMe_3)_2$ (**2.14**) in the Lit.

R =	PhC≡C	c-C_6H_{11}	Ph	2-Thienyl	1-Naphthyl
Yield (%) =	86	77	82	84	93
Yield (%)* =	61	52	75	67	52

*Yields of $RCH_2N(SiMe_3)_2$ in the previous work [84CC794][84AG(E)53] using $MeO\text{-}CH_2\text{-}N(SiMe_3)_2$

2.3 Experimental

Melting points were determined with a Kofler hot stage apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR 300 MHz spectrometer in DMSO using TMS as an internal reference for ^1H spectra and DMSO for ^{13}C NMR spectra (abbreviation used: s singlet, d doublet, t triplet, q quartet, m multiplet).

2.3.1 Representative Procedures for the Preparation of Primary Amine Hydrochlorides **2.17**. Method A, One-pot Conversion of Betmip to **2.17**

2-Phenylethylamine hydrochloride (**1.5a**). Benzylmagnesium chloride (15 mmol) in diethyl ether (30 ml) was added to a stirring solution of betmip (12 mmol) in

THF (25 ml) over 20 min. The reaction mixture was stirred overnight at room temperature, saturated with ammonium chloride (15 ml), then concentrated ammonium hydroxide (20 ml) was added. After stirring for 1 hr the mixture was extracted with diethyl ether (3 x 60 ml). The combined organic phase was washed with 1 M NaOH (2 x 15 ml), dried ($MgSO_4$) and the solvent evaporated. The residue was dissolved in anhydrous diethyl ether (20 ml) and the saturated ethereal HCl (20 ml) solution was added to precipitate the amine hydrochloride. The product was filtered off, washed with anhydrous diethyl ether and ethyl acetate to give a white solid (1.23 g, 67%, m.p.: 220-221°C). ^{1}H NMR 3.01 (m, 4 H), 7.35-7.23 (m, 5 H), 8.38 (s, 3 H); ^{13}C NMR 30.93, 38.14, 124.52, 126.43, 126.49, 135.31.

2.3.2 Representative Procedures for Preparation of Primary Amine Hydrochlorides **2.17**. Method B, One-pot Conversion of Benzotriazol-1-ylmethyl Azide to **2.17**

Benzylamine hydrochloride (**2.17b**). Triphenylphosphine (2.1 g, 8 mmol) in THF (15 ml) was added to a solution of benzotriazol-1-ylmethyl azide (1.4 g, 8 mmol) in THF (15 ml). After stirring for 10 min until no further nitrogen evolution could be observed, phenylmagnesium chloride (10 mmol) in diethyl ether (25 ml) was added dropwise over 20 min. The same work-up as in Method A then gave benzylamine hydrochloride (**2.17b**) (0.95 g, 82%, m.p. 255-256°C). ^{1}H NMR 4.02 (m, 2 H), 7.36-7.56 (m, 5 H), 8.74 (s, 3 H); ^{13}C NMR 40.28, 126.20, 126.33, 126.94, 131.73.

Tridecylamine hydrochloride (**2.17c**). ^{1}H NMR 0.88 (t, J = 7 Hz, 3 H), 1.31-1.24 (m, 20 H), 1.65 (m, 2 H), 8.19 (s, 3 H); ^{13}C NMR 12.55, 20.89, 24.85, 25.72, 27.35, 27.53, 27.67, 27.76, 27.83, 27.86, 29.28, 30.11, 37.91.

Phenylpropargylmethylamine hydrochloride (**2.17d**). ^{1}H NMR 3.97 (s, 2 H),

7.48-7.40 (m, 5 H), 8.75 (s, 3 H); ^{13}C NMR 20.93, 80.48, 80.61, 119.31, 126.64, 127.06, 129.39.

Cyclohexylmethylamine hydrochloride (**2.17e**). ^{1}H NMR 1.0-0.85, 1.10-1.30, 1.79-1.61, (m, 11 H), 2.62 (d, J = 7 Hz, 2 H), 8.17 (s, 3 H); ^{13}C NMR 23.00, 23.59, 27.80, 33.26, 42.39.

(2-Thienyl)methylamine hydrochloride (**2.17f**). ^{1}H NMR 4.22 (s, 2 H), 7.49 (m, 1 H), 7.32 (m, 1 H), 7.04 (m, 1 H), 8.70 (s, 3 H); ^{13}H NMR 34.76, 124.94, 125.11, 127.09, 133.03.

1-Naphthylmethylamine hydrochloride (**2.17g**). ^{1}H NMR 4.50 (s, 2 H), 7.45-8.15 (m, 7 H), 8.85 (s, 3 H); ^{13}C NMR 39.63, 131.05, 123.75, 125.63, 126.85, 127.04, 127.70, 128.96, 129.36, 130.16, 131.05, 133.56.

CHAPTER III
BETMIP, A NOVEL SYNTHON OF $^{+}CH_2N=$: APPLICATION TO ONE-POT SYNTHESES OF CARBODIIMIDES, IMINES, ISOTHIOCYANATES, AZIRIDINES AND SECONDARY AMINES

3.1 Introduction

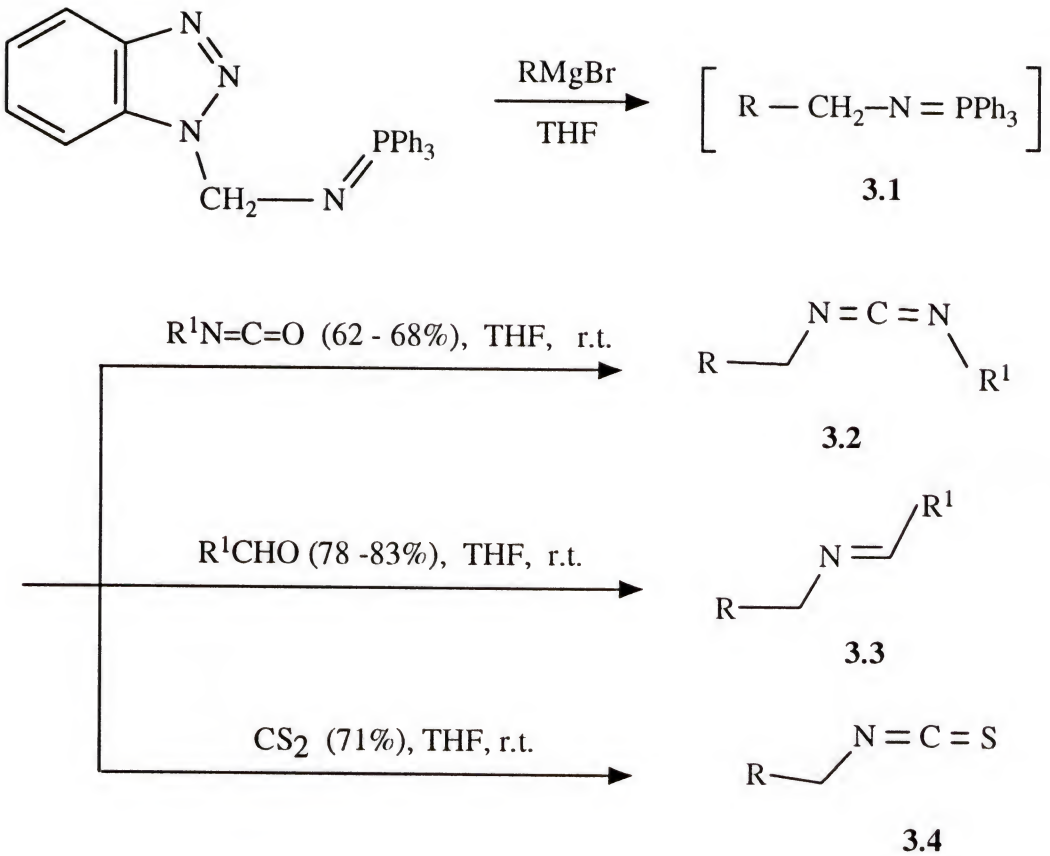
Since the first reported synthesis of iminophosphoranes by the reaction of a tertiary phosphine with organic azides [19CB635], numerous articles have appeared on synthetic applications of N=P compounds [55LAC117][60CB405] [30CB1176] [74CB1590]. Iminophosphoranes possess similar structural and chemical characteristics to those of phosphorus ylides, and are shown to react with carbonyl compounds to form Schiff bases and phosphine oxide [19CB635]. Iminophosphoranes also react with carbon dioxide and carbon disulfide to yield isocyanates and isothiocyanates, respectively [21CB861]. Further successful transformations of N-substituted iminophosphoranes by reactions with acids [84TL4841] [89JCS(P1)1], water [59AG626] [83TL763], alkyl halides [63JOC483] [70JOC2826] [83CB1691], oxiranes [78JOC4271] [76TL4003] [76CB814], nitrosyl chloride [63AG574], acetylenedicarboxylates [64JPC(L)87] and ozone [84JA3682], demonstrate their versatility in organic synthesis. Recently N-substituted triphenyliminophosphoranes have been used in Diels-Alder reactions [81TL4607] [79H949] and in syntheses of heterocyclic compounds [69LAC29] [86CL493] [86H2437] [82CC1224] [86S843] [86CL1549] [86S772] [85S304] [85TL793] [81JOC3562]. The N-alkyl or arylsubstituted iminophosphoranes utilized were almost invariably synthesized by Staudinger's method [81T437] (the reaction of triphenylphosphine with the

corresponding azide). There are a few preparations of iminophosphoranes from amines [66JOC2894] [70BCJ1160], amides [85JOC1712]], and also isoxazoles [83JHC899] [74CL575], which have some synthetic value. We now describe the first examples in which N=C compounds are prepared from N-substituted iminophosphoranes derived from Grignard reactions.

3.2 Results and Discussion

The previous chapters described the preparation of betmip and its application to the synthesis of primary amines in high yields. Although the reactions were carried out in one-pot, the reactions with Grignard reagents and the hydrolysis steps were performed consecutively, i.e. there was no reaction between the Grignard reagent and the N=P bond. Thus after the Grignard step, the N=P intermediate could undergo other iminophosphorane reactions with some of the carbonyl groups, *in situ*, to yield various other types of C=N compounds.

As shown in Scheme 3.1, the intermediates were successfully used to synthesize unsymmetrical carbodiimides **3.2**, Schiff bases **3.3**, isothiocyanates **3.4**. In each case the formation of the new functionality is accompanied by a one-carbon homologation of the original hydrocarbon moiety (R) of the Grignard reagent. Displacement of the benzotriazole moiety in betmip by the Grignard reagent could be clearly monitored by the precipitation of the magnesium salt of benzotriazole, which was complete at room temperature, or even at 0°C, in a few minutes. The formed magnesium salt of benzotriazole was conveniently removed by filtration, and this is especially advantageous in the preparation of water-sensitive carbodiimides and isothiocyanates. However, even if it was not removed, this salt did not appear to affect



Compd	R	R^1	Compd	R	R^1
3.2a	Me	t-Butyl	3.3a	Ph	Ph
3.2b	Me	Ph	3.3b	Me	Ph
3.2c	Ph	t-Butyl	3.3c	Ph	i-Pr
3.2d	Ph	1-Naphthyl	3.4	Ph	---

Scheme 3.1

the iminophosphorane reactions under the conditions employed. For example, when two molar equivalents of phenyl isocyanate were added to the reaction mixture from methylmagnesium iodide and betmip, a 1:1 (NMR) mixture of phenyl isocyanate (starting material) and Ethylphenylcarbodiimide (**3.2b**) was isolated; no reaction between the isocyanate and the benzotriazolate salt could be detected. The one-pot method could be used for most of the transformations shown in Scheme 3.1. The reaction mixture of the Grignard reagent and the iminophosphorane **3.1** was treated with either (i) an isocyanate, or (ii) an aldehyde, or (iii) carbon disulfide. After removal of the benzotriazolate magnesium salt by filtration, the products were isolated from the side product triphenylphosphine oxide by distillation. The results are shown in Table 3.1. The procedure is assumed to follow the Wittig reaction mechanism *i.e.* nucleophilic addition of the N=P group to the carbonyl group followed by an elimination of triphenylphosphine oxide *via* the process shown in Fig 3.1.

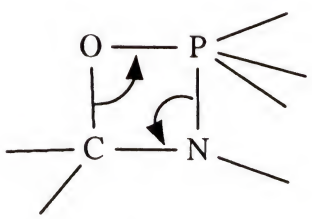


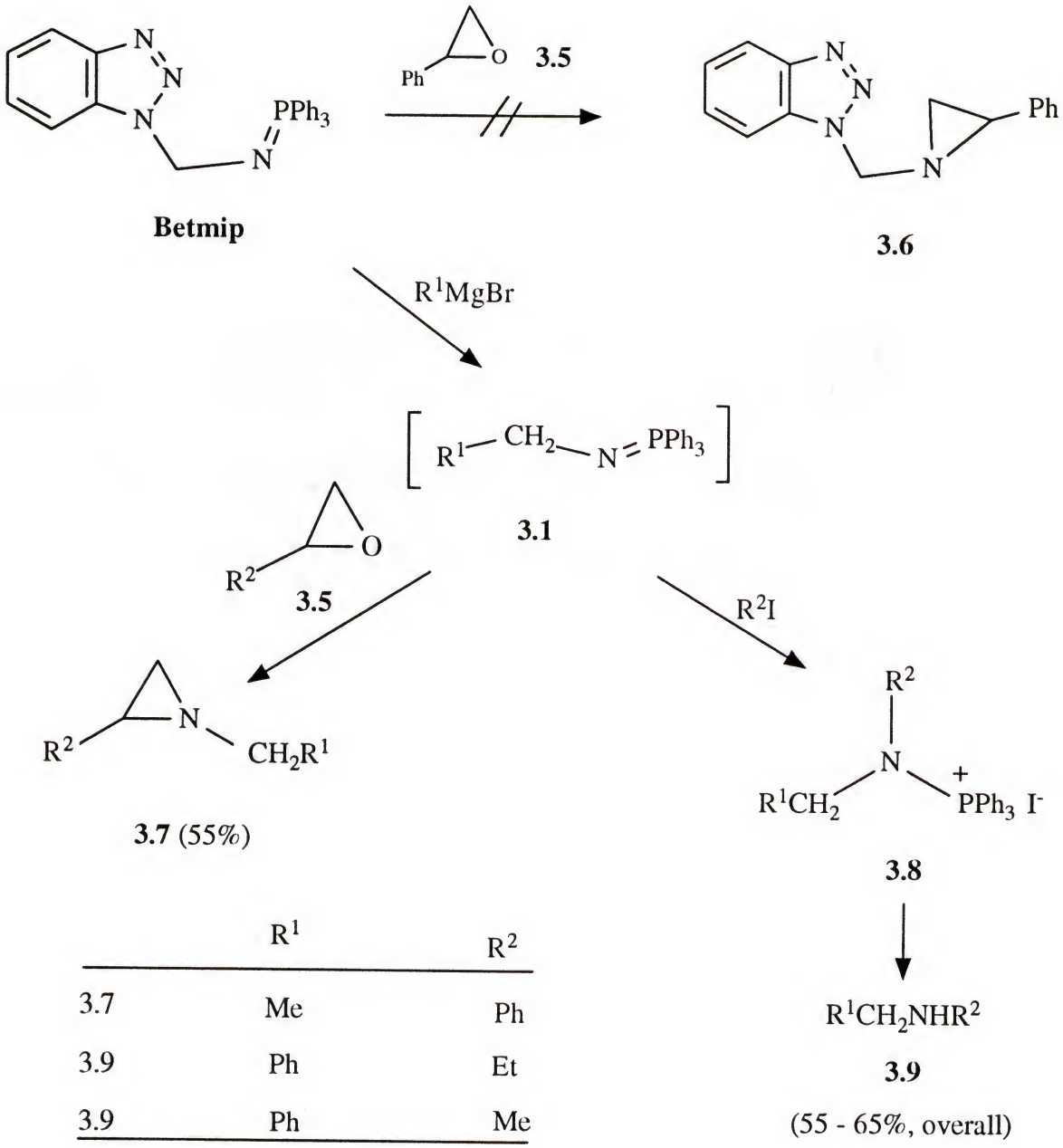
Fig . 3.1

Other than the reactions with the C=O and C=S groups as above, the iminophosphorane **3.1** formed *in situ* could be converted to an aziridine **3.7** by styrene epoxide (**3.5**) in refluxing THF in a moderate yield, Scheme 3.2. This type of reaction can also be explained by the mechanism described above for the reaction with carbonyl compounds. However, attempts to get the intermediate **3.6** by a reaction of betmip with styrene epoxide (**3.5**) were unsuccessful. All starting materials were recovered after refluxing betmip and styrene epoxide (**3.5**) in THF for 24 hrs. Presumably the

electron-withdrawing benzotriazole group reduced the nucleophilicity of the N=P group in betmip which is not strong enough to open the epoxide ring. This result allowed us to explain why betmip is much more stable than other iminophosphoranes **3.1** as mentioned in Chapter I.

The phosphonium salts **3.8** were prepared from the reaction of the iminophosphorane **3.1** with alkyl halides at room temperature and were transformed to the secondary amines **3.9** by refluxing aqueous sodium hydroxide in good yields. The hydrolysis could be monitored by the disappearance of the solid phosphonium salts **3.8**.

In summary, our new method for the preparation of N-substituted iminophosphoranes from 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (betmip) has several advantages and offers versatile applications in organic synthesis. Betmip, a crystalline solid, can be conveniently prepared from benzotriazole on a large scale and in a high overall yield. It is stable at room temperature for at least several months. Reactions with easily accessible (often commercially available) Grignard reagents formed a range of N-substituted iminophosphoranes, which were conveniently transformed, without isolation and in high yields, into diverse nitrogen-containing compounds as exemplified by carbodiimides **3.2**, Schiff bases **3.3**, isothiocyanates **3.4**, aziridines **3.7**, and secondary amines **3.9**. The reactions were clean; NMR spectra of the isolated crude products showed no side products except triphenylphosphine oxide and benzotriazolate magnesium salt. Finally, this method has provided the first examples of one-carbon homologation of N-substituted iminophosphoranes from carbanions.



	R^1	R^2
3.7	Me	Ph
3.9	Ph	Et
3.9	Ph	Me

Scheme 3.2

Table 3.1 Preparation of Carbodiimides **3.2**, Schiff Bases **3.3** Isothiocyanates **3.4**, Aziridines **3.7** and Secondary Amines **3.9**

Compd	Yield (%)[a]	b..p (°C / mmHg) [b]	Lit. b.p. (°C /mmHg)
3.2a	61	80 - 82 / 105	137 -139 / 62 [63AG164]
3.2b	62	95 - 97 / 2.0	43 / 0.05 [68JCS(C)2640]
3.2c	65	95 - 97 / 0.8	123 -125 / 23 [63AG164]
3.2d	85[c]	oil	--------
3.3a	83[c]	oil	105 / 20 [29MI(12)104]
3.3b	78	54 - 55 / 0.7	207 / 144 [25MI(7)213]
3.3c	68	82 - 84 / 1.2	--------
3.4a	71	98 - 100 / 3.5	140 -141 / 17 [29MI(12)1059]
3.7	55	55 - 57 / 0.6	68 - 72 / 2.5 [76CB814]
3.9a	65 [d,e]	167.5 - 168.5 (mp)	169 (mp) [29MI(12)1020]
3.9b	55 [e]	40 -42 / 0.7	184 -185 / 749 [29MI(12)1019]

a. Based on the distilled product
b. Not corrected
c. After column chromatography
d. Yield of hydrocloride salt
e. Overall yield, the intermediate phosphonium salts were isolated in 78% **3.8a** and 83% **3.8b**

Table 3.2 Molecular Fragments in HRMS of Carbodiimides **3.2**, Schiff Bases **3.3**, Isothiocyanates **3.4**, Aziridines **3.7** and Secondary Amines **3.9**

Compd	Formula	Required	Found
3.2a	$C_7H_{14}N_2$	126.1157	126.1158
3.2b	$C_9H_{10}N_2$	146.0884	146.0884
3.2c	$C_9H_{10}N_2$	188.1314	188.1330
3.2d	$C_{18}H_{14}N_2Cl$	258.1157	258.1158
3.3a	$C_{14}H_{13}N$	195.1048	195.1056
3.3b	$C_9H_{13}N$	133.0892	133.0894
3.3c	$C_{11}H_{15}N$	161.1204	161.1206
3.4a	C_7H_8NS	149.0299	149.0293
3.7	$C_{10}H_{13}N$	147.1048	147.1049
3.9a	$C_9H_{14}NCl$	---------	---------
3.9b	$C_8H_{11}N$	121.0991	121.0889

3.3 Experimental

Melting points were determined with a Kofler hot-stage apparatus, and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 (300 Hz or 75 Hz, FT mode) spectrometer in $CDCl_3$ or DMSO-d_6. An internal standard TMS (δ = 0.0) was used for ^{1}H NMR spectra and the solvent signals ($CDCl_3$, δ = 77.0; or DMSO-d_6, δ = 39.5) for ^{13}C NMR spectra. HRMS were recorded on an AEI MS-30 mass spectrometer.

3.3.1 General Procedure for Carbodiimides **3.2**, Schiff Bases **3.3**, Isothiocyanates **3.4**, and Aziridines **3.7**

To a solution of betmip (5.0 g, 12.2 mmol) in dry THF (50 ml), a commercial Grignard reagent (solution in THF, 13 mmol) was added at room temperature over 5 min. Precipitation of a white solid occurred almost instantaneously. The suspension was stirred at room temperature for 5 hrs, then the appropriate reagent either (i) isocyanates for carbodiimides **3.2** (12.2 mmol), or (ii) aldehydes for Schiff bases **3.3** (12.2 mmol), or (iii) CS_2 for isothiocyanates **3.4** (40 mmol), or (iv) styrene oxide for aziridine **3.7** (12.2 mmol) was added and stirring continued overnight (for compounds **3.2**, **3.3** and **3.4**), or the reaction mixture refluxed for 48 hrs (for aziridine **3.7**). The mixture was diluted with anhydrous Et_2O (50 ml), the precipitate was filtered and washed with anhydrous Et_2O. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give a mixture of triphenylphosphine oxide and the desired product, which was isolated by vacuum distillation (**3.2a-c**, **3.3b**, **3.3c**) or column chromatography for the other.

t-Butylethylcarbodiimide (**3.2a**). ^{1}H NMR 1.15 (t, 3 H, CH_3), 1.29 (s, 9 H, t-Bu), 3.25 (q, 2 H, CH_2); ^{13}C NMR 16.4, 30.9, 41.2 (CH_2), 54.5, 139.9.

Ethylphenylcarbodiimide (**3.2b**). ^{1}H NMR 1.28 (t, 3 H, CH_3), 3.36 (q, 2 H, CH_2), 7.01-7.20 (m, 5 Harom); ^{13}C NMR 16.8, 41.6 (CH_2), 123.3, 124.5, 129.2, 136.1, 140.6

t-Butylbenzylcarbodiimide (**3.3c**). ^{1}H NMR 1.12 (s, 9 H, $C(CH_3)_3$), 4.30 (s, 2 H, CH_2), 7.20-7.45 (m, 5 Harom); ^{13}C NMR 30.9, 50.6 (CH_2), 55.0, 127.3, 127.8, 128.3, 138.6, 140.5.

1-Naphthylbenzylcarbodiimide (**3.2d**). ^{1}H NMR 4.50 (s, 2 H, CH_2), 7.10-8.20 (m, 12 Harom); ^{13}C NMR 50.1 (CH_2), 119.7, 123.2, 124.5, 125.5, 125.7, 126.2,126.9, 127.1, 127.5, 128.3, 128.5, 134.0, 136.2, 137.6, 140.2.

N-Benzylidenebenzylamine (**3.3a**). ^{1}H NMR 4.65 (s, 2 H, CH_2), 7.10-7.78 (m, 10 Harom), 8.14 (s, 1 H, =CH); ^{13}C NMR 67.4 (CH_2), 126.8, 127.8, 128.2, 128.3, 128.4, 130.5, 136.1, 139.3, 161.6.

N-Benzylideneethylamine (**3.3b**). ^{1}H NMR 1.28 (t, 3 H, CH_3), 3.60 (s, 2 H, CH_2), 7.33-7.72 (m, 5 Harom), 8.22 (s, 1 H, =CH); ^{13}C NMR 16.1, 55.6 (CH_2), 127.7, 128.3, 130.2, 136.1, 160.1.

N-Isobutylidenebenzylamine (**3.3c**). ^{1}H NMR 1.1 (d, 6 H, $C(CH_3)_2$), 2.5 (m, 1 H, $CH(CH_3)_2$), 4.52 (s, 2 H, CH_2), 7.20-7.40 (m, 5 Harom), 7.6 (m, 1 H, =CH); ^{13}C NMR 19.1, 33.8, 64.4 (CH_2), 127.5, 128.2, 131.8, 139.5, 170.8.

Benzyl isothiocyanate (**3.4**). ^{1}H NMR 4.63 (s, 2 H, CH_2), 7.20-7.40 (m, 5 Harom); ^{13}C NMR 48.5 (CH_2), 126.6, 128.2, 128.8, 134.0, 141.1.

1-Ethyl-2-phenylaziridine (**3.7**). ^{1}H NMR 1.17 (t, 3 H, CH_3), 1.63 (d, 1 H, J = 6.5), 1.88 (d, 1 H, J = 3), 2.29 (q, 1 H, J = 3), 4.63 (q, 2 H, CH_2), 7.15-7.30 (m, 5

Harom); ^{13}C NMR 14.4, 37.4 (CH_2), 41.1, 55.8, 126.1, 126.7, 128.1, 140.3.

3.3.2 Procedure for the Preparation of Secondary Amines **3.9a** and **3.9b**

To a solution of betmip (10 g, 25 mmol) in dry THF (150 ml) commercial phenylmagnesium bromide (2 M in THF, 12.5 ml, 25 mmol) was added at room temperature. The suspension was stirred for 5 hrs, then a solution of (i) iodoethane (12.7 g, 83 mmol) for **3.9a**, or (ii) iodomethane (11.3 g, 81 mmol) for **3.9b**, in dry THF (35 ml) was added. The reaction mixture was stirred overnight, and filtered. The solid was washed with saturated $NH_4Cl_{(aq.)}$ then with Et_2O, and dried to give phosphonium salt **3.8a** (10.1 g, 78%) or **3.8b** (9.0 g, 73%), respectively. The phosphonium salt was heated under reflux in aq NaOH (5 M, 250 ml) for 10 hrs. The product was extracted with Et_2O (3 x 40 ml), the combined ethereal solution was washed with water (2 x 20 ml), dried ($MgSO_4$) and the solvent removed. Secondary amine **3.9a** was isolated as the hydrochloride salt by treating the residue with the saturated ethereal HCl solution (50 ml). The resulting precipitate was collected by filtration and washed with acetone. Secondary amine **3.9b** was isolated by vacuum distillation.

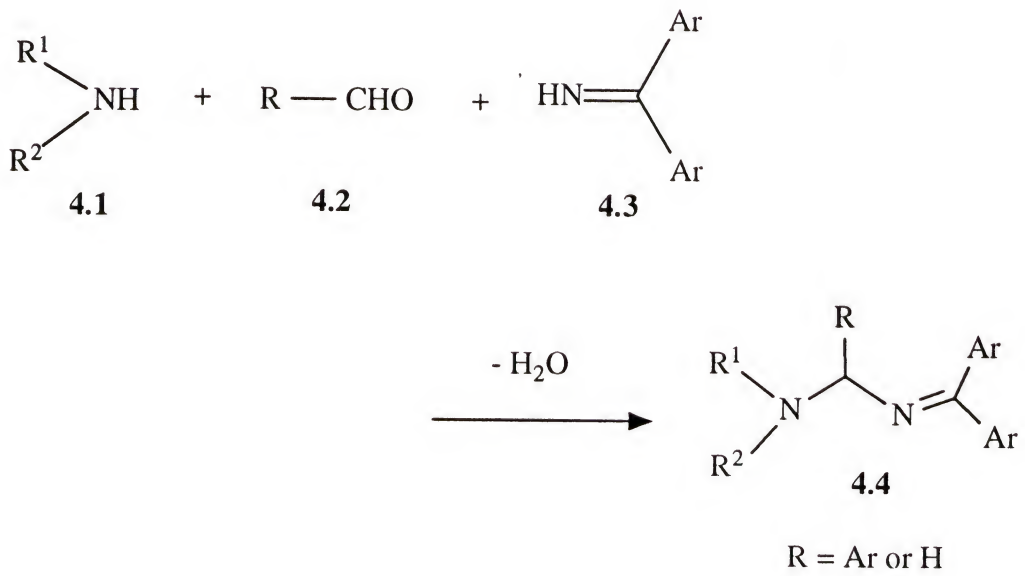
Ethylbenzylamine hydrochloride (**3.9a**). ^1H NMR 1.30 (t, 3 H, CH_3), 2.83-3.02 (m, 2 H, CH_3), 4.11 (t, 2 H, CH_2), 7.39-7.66 (m, 5 H arom), 9.38(br, s, 2 H, NH_2); ^{13}C NMR 11.0, 41.0, 50.0 (CH_2), 128.9, 129.2, 130.0, 130.2.

Methylbenzylamine (**3.9b**). ^1H NMR 1.32(s, 1 H, NH), 2.42 (s, 3 H, CH_3), 3.71 (m, 2 H, CH_2), 7.20-7.35 (m, 5 Harom); ^{13}C NMR 35.8, 55.9 (CH_2), 126.7, 127.9, 128.1, 140.0.

CHAPTER IV
BETMIP, APPLICATION TO ONE-POT SYNTHESIS OF α-(ARYLIDENEAMINO)ALKYLAMINES

4.1 Introduction

Although alkyl diamines (aminals) are well documented compounds, the corresponding unsaturated α-(diarylideneamino)alkylamines (**4.4**) have only been mentioned once in the literature [78LAC1928] where they were prepared by a Mannich condensation between diarylketimines **4.3**, secondary amines **4.1** and formaldehyde or aryl aldehydes **4.2** (Scheme 4.1). Diarylketimines **4.3** require drastic conditions for their preparation, such as the use of sealed tubes at high temperature [30JA820] or the use of molten ketones [46JA846]. Other imines with hydrogens on the nitrogen atoms spontaneously polymerize [70MI67].

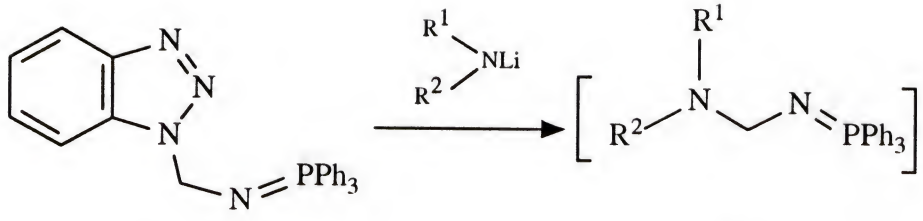


Scheme 4.1

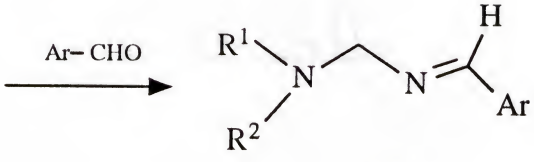
1-(Triphenylphosphoroylideneaminomethyl)benzotriazole (betmip) is a new reagent. Previous chapters have demonstrated the usefulness of betmip in the novel synthesis of primary amines, and in the preparation of carbodiimides, imines, isothiocyanates, aziridines and secondary amines. We now report a new route to α-(arylideneamino)alkylamines (**4.6**) *via* nucleophilic displacement of the benzotriazole moiety from betmip with lithium amides, and condensation of the resulting iminophosphorane intermediates **4.5** with aryl aldehydes (Scheme 4.2).

4.2 Results and Discussion

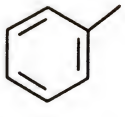
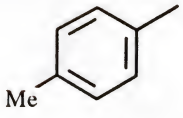
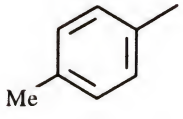
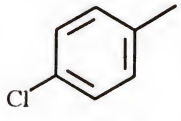
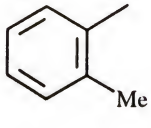
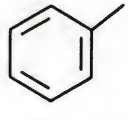
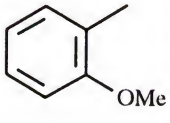
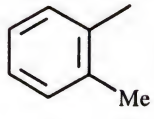
The reaction was carried out in one pot. The lithium amides were generated *in situ* from the corresponding secondary amines and butyllithium. The resulting suspension was stirred with betmip to form the N-(N′,N′-dialkyl-aminomethyl)iminophosphoranes **4.5**, the formation of which was confirmed by the further reaction with an aryl aldehyde, Scheme 4.2. The work up and isolation procedures were straight forward. After removal of the lithium salt of benzotriazole by filtration, the products were separated from the triphenylphosphine oxide side product by distillation. The structures of the products were characterized by the ^{1}H and ^{13}C NMR spectra and supported by the high resolution mass spectra (Table 4.1). In the NMR spectra, the distinctive proton signals for the CH_2 group, the formaldehyde residue, were at 4.20-5.20 ppm, and the carbon signals were at 75-82 ppm. Low field signals (7.6-8.5 ppm) were observed for CH=N protons showing overlap with phenyl-ring proton signals. The carbon signals of the imine group showed the expected chemical shifts (159-161 ppm). Mass spectrometric analysis (Table 4.1) of each product gave a characteristic peak resulting from the molecular ion and two



betmip **4.5**



4.6

Compd	R^1	R^2	Ar	Compd	R^1	R^2	Ar
4.6a	Me	Ph		4.6e	Pyrrolidine		
4.6b	Me	Ph		4.6f	Pyrrolidine		
4.6c	Me	Ph		4.6g	Morpholine		
4.6d	Pyrrolidine			4.6h	Morpholine		

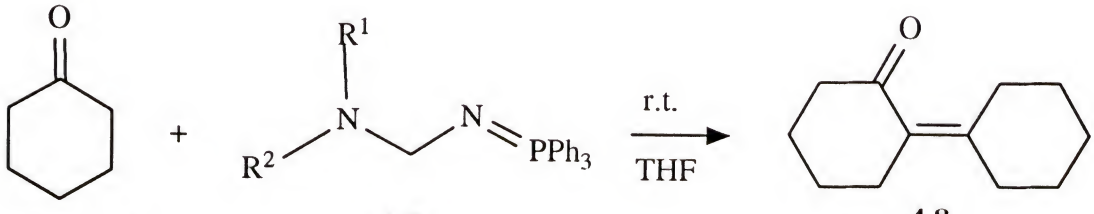
Scheme 4.2

Table 4.1 Preparation of α-(Arylideneamino)alkylamines (**4.6**)

No	Yield (%)	b.p. (°C/mmHg)	Molecular Formula High Res. MS (calc.)	Mass Spectra (70ev)
4.6a	73	162-166 / 0.9	$C_{15}H_{20}N_2$ 224.1306 (224.1313)	224 (M^+,7%); 120 (100%); 106 (5%); 91 (26%)
4.6b	70	186-171 / 0.5	$C_{16}H_{22}N_2$ 238.1479 (238.1475)	238 (M^+, 9%); 132 (11%); 120 (100%); 118 (2%); 106 (14%); 105 (21%).
4.6c	54	170-174 / 0.5	$C_{16}H_{22}N_2$ 238.1479 (238.1475)	238 (M^+, 7%); 131 (15%); 120 (100%); 118 (5%); 105 (29%).
4.6d	57	145-149 / 1.2	$C_{13}H_{18}N_2O$ 218.1410 (218.1419)	218 (M^+, 1%); 148 (29%); 134(14%); 121 (57%); 84 (100%).
4.6e	64	126-130 / 1.2	$C_{13}H_{18}N_2$ 202.1485 (202.1470)	202 (M^+, 0.4%); 132 (14); 119 (12%); 105 (14%); 84 (100%).
4.6f	45	119-122 / 0.3	$C_{12}H_{16}N_2Cl$ 223.0002 (222.9990)	222 (M^+, 0.6%); 152 (5%); 139 (20%); 125 (30%); 84 (100%).
4.6g	43	121-124 / 0.4	$C_{12}H_{16}N_2O$ 204.1263 (204.1263)	204 (M^+, 2%); 176 (37%); 118 (64%); 91 (100%); 104 (25%).
4.6h	51	138-141 / 0.5	$C_{13}H_{18}N_2O$ 218.1416 (218.1419)	218 (M^+, 0.5%); 190 (100); 130 (20%); 105 (65%).

fragmentation ions resulting from cleavage of both N-CH_2-N bonds. Products (**4.6a-f**) showed the base peaks of $R^1R^2N^+=CH_2$ fragments, while the morpholine derivatives gave a base peak 91 (m/z) from **4.6g** and 190 (m/z) from **4.6h**. Presumably they were formed by McLafferty rearrangements followed by cleavage of the $ArCH_2$-N bond for **4.6g** or loss of the CH_2=N unit for **4.6h**.

In summary, our new method for the preparation of α-(arylidene-amino)alkylamines (**4.6**) from 1-(triphenylphosphoroylideneaminomethyl)-benzotriazole (betmip) offers a new convenient route to this novel class of compounds. The availability of compounds of type **4.6** has extended the range of animal functionality, and offered interesting potential substrates for studies of physiological activity, of conformation, and of basicity. It should be noted that N-(N′,N′-dialkylaminomethyl)iminophosphoranes (**4.5**) showed considerable basicity, thus attempts to extend this reaction to enolizable aldehydes or ketones resulted only in aldol condensation products.



4.7 **4.5** **4.8**

Scheme 4.3

4.3 Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal reference for ^{1}H spectra and $CDCl_3$ for ^{13}C NMR spectra (abbreviations used: s singlet, d doublet, m multiplet). Mass spectra were recorded at 70 ev on an AEI MS-30 mass spectrometer. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl. 1-(Triphenylphosphoroylideneaminomethyl)benzotriazole (betmip) was prepared by the procedure as discussed in Chapter I.

4.3.1 General Procedure for the Preparation of α-(Arylideneamino)alkylamines (**4.6**)

Butyllithium (5.6 ml, 14 mmol, 2.5 M solution in hexanes) was added to a stirred solution of a secondary amine (14 mmol) in THF (50 ml) at -78°C under argon. A solution of betmip (6.5 g, 16 mmol) in THF (30 ml) was added and stirring continued at room temperature for 20 hrs during which time a precipitate appeared. The aldehyde (14 mmol) in THF (15 ml) was then added and the resulting solution stirred for a further 15 hrs. After removal of THF under reduced pressure, the crude product was dissolved in anhydrous diethyl ether and the insoluble by-products filtered off. The solid by-products were washed several times with anhydrous diethyl ether, the diethyl ether portions combined, and diethyl ether removed to give an oily product. Distillation under vacuum gave the pure α-(arylideneamino)alkylamines (**4.6**).

N-Methyl-N-phenyl(benzylideneaminomethyl)amine (**4.6a**). ^{1}H NMR 3.05 (s, 3 H), 5.22 (s, 2 H, CH_2), 6.75 (m, 3 H), 7.2 (m, 3 H), 7.4 (m, 3 H), 7.75 (m, 2 H); ^{13}C NMR 38.2, 75.4 (CH_2), 112.4, 117.3, 128.5, 128.3, 129.1, 130.7, 135.8, 148.7, 158.2 (CH=N).

N-Methyl-N-phenyl(4-methylbenzylideneaminomethyl)amine (**4.6b**). ^{1}H NMR 2.3 (s, 3 H), 3.0 (s, 3 H), 5.15 (s, 2 H CH_2), 6.7 (m, 3 H), 7.15 (m, 2 H), 7.2 (m, 2 H), 7.6 (m, 2 H); ^{13}C NMR 21.2, 37.9, 75.2 (CH_2), 112.2, 117.1, 128.1, 128.9, 129.0, 133.1, 140.7, 148.5, 158.0.

N-Methyl-N-phenyl(2-methylbenzylideneaminomethyl)amine (**4.6c**). ^{1}H NMR 2.35 (s, 3 H), 3.05 (s, 3 H), 5.20 (s, 2 H, CH_2), 6.70 (m, 3 H), 7.2 (m, 5 H), 7.85 (m, 1 H); ^{13}C NMR 19.1, 38.0, 75.6 (CH_2), 112.4, 117.3, 126.0, 129.0, 127.4, 130.1, 130.6, 133.8, 137.6, 148.5, 157.1.

N-(2-Methoxybenzylideneaminomethyl)pyrrolidine (**4.6d**). ^{1}H NMR 1.75 (m, 4 H), 2.7 (m, 4 H), 2.35 (s, 3 H), 4.40 (s, 2 H, CH_2), 6.9 (m, 2 H), 7.3 (m, 1 H), 8.05 (m, 1 H); ^{13}C NMR 23.5, 23.1, 50.8, 52.4, 55.1, 79.3 (CH_2), 110.6, 120.3, 127.1, 131.6, 124.0, 128.2, 156.7.

N-(4-Methylbenzylideneaminomethyl)pyrrolidine (**4.6e**). ^{1}H NMR 1.8 (m, 4 H), 2.7 (m, 4 H), 2.35 (s, 3 H), 4.40 (s, 2 H, CH_2), 7.2 (d, 2 H, J = 8 Hz), 7.65 (d, 2 H, J = 8 Hz); ^{13}C NMR 21.3, 23.6, 51.0, 79.2 (CH2), 128.2, 129.1, 133.2, 140.8, 160.8.

N-(4-Chlorobenzylideneaminomethyl)pyrrolidine (**4.6f**). ^{1}H NMR 1.75 (m, 4 H), 2.75 (m, 4 H), 4.45 (s, 2 H, CH_2), 7.35 (d, 2 H, J = 8 Hz), 7.7 (d, 2 H, J = 8 Hz); ^{13}C NMR 23.6, 51.1, 79.0 (CH_2), 128.3, 128.7, 129.4, 130.4, 159.5.

N-(Benzylideneaminomethyl)morpholine (**4.6g**). ^{1}H NMR 2.65 (m, 4 H), 3.75 (m, 4 H), 4.27 (s, 2 H, CH_2), 7.4 (m. 3 H), 7.75 (m, 2 H); ^{13}C NMR 50.9, 66.6, 82.3 (CH_2), 128.1, 128.3, 130.7, 135.3, 161.2.

N-(2-Methylbenzylideneaminomethyl)morpholine (**4.6h**). ^{1}H NMR 2.5 (s, 3 H), 2.7 (m, 4 H), 3.8 (m, 4 H), 4.3 (s, 2 H, CH_2), 7.2 (m, 3 H), 7.9 (m, 1 H); ^{13}C NMR 19.3, 50.9, 66.7, 82.3, 125.9, 127.9, 130.3, 130.7, 133.4, 137.7, 160.1.

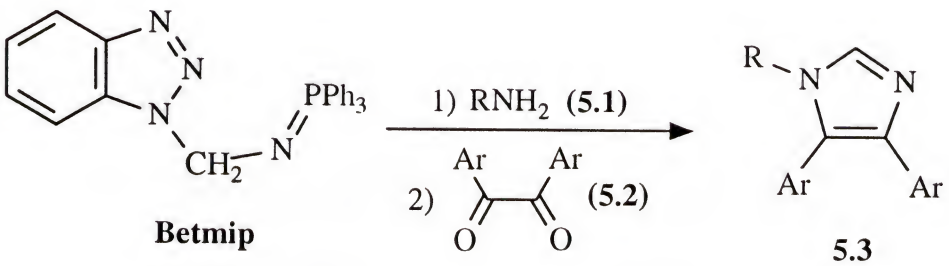
CHAPTER V
BETMIP, APPLICATION TO ONE-POT SYNTHESIS OF 1,4,5-TRISUBSTITUTED IMIDAZOLES

5.1 Introduction

Betmip, 1-(triphenylphosphoroylideneaminomethyl)benzotriazole is a new synthon of considerable utility. In previous chapters, the usefulness of betmip in a novel synthesis of primary amines, and in the preparation of carbodiimides, imines, isothiocyanates, aziridines, secondary amines and α-(arylideneamino)alkylamines has been discussed. The present work is concerned with the application of betmip to the synthesis of 1,4,5-trisubstituted imidazoles from primary amines and α-diketones. Substituted imidazoles, many of which play important roles in the biologically significant processes, have been prepared by a variety of synthetic methods [84MI457] [70MI103]. Although most substitution patterns can be realized by these methods, few simple, straightforward routes to 1,4,5-trisubstituted imidazoles have been reported. Such imidazoles have been synthesized by novel cycloadditions of α-tosylbenzyl isocyanide with aldimines, exemplified by reactions of TosMIC derivatives [77JOC1153], and by the dimerization of N-methyl-C-phenylnitrone in the presence of potassium cyanide to give 1-methyl-4,5-diphenylimidazole [75TL2717]. Many methods of imidazole synthesis, such as the classical Radziszewski reaction, involve the use of α-functionalized carbonyl compounds such as α-diketones and ammonia with or without added aldehyde [59CB338]. Formamide is a convenient substitute for ammonia, and in the presence of formic acid 4,5-disubstituted imidazoles are formed [53CB88] from diaryl ketones, although ketones possessing α-hydrogens undergo self-condensation reactions.

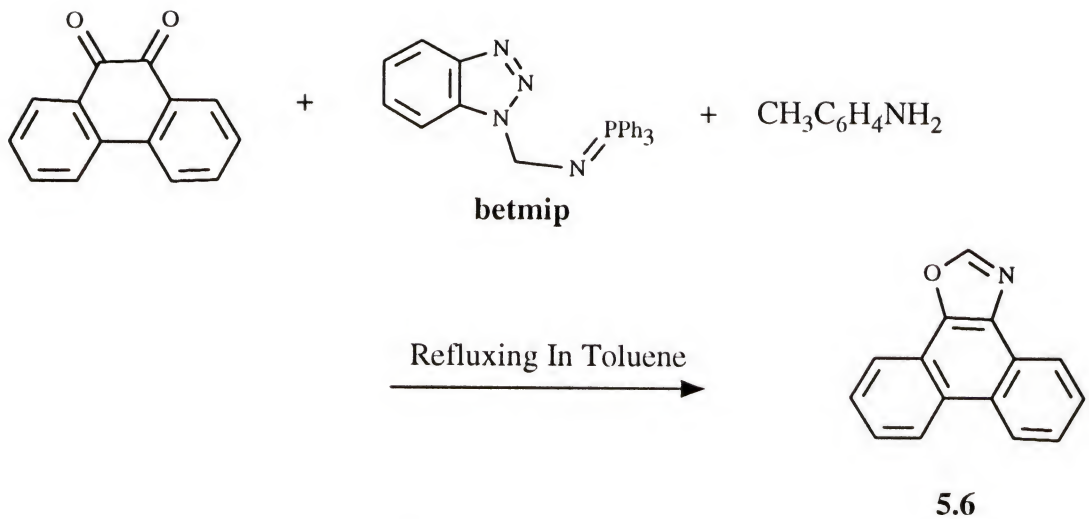
5.2 Results and Discussion

The betmip molecule undergoes reactions with primary amines and 1,2-diaryl α-diketones to give 1,4,5-trisubstituted imidazoles **5.3** in good yields (Scheme 5.1 and Table 5.1). The reactions were carried out in one-pot, without isolation of **5.4**, and



Scheme 5. 1

the work up and isolation procedures were straightforward. The use of various primary aliphatic amines **5.1** and α-diketones **5.2** such as benzil and phenanthraquinone gave good results, and the reaction was successfully extended to 4-dimethylaminoaniline. In this case the activation by the strongly electron donating dimethylamino group was essential. Use of the less nucleophilic p-toluidine, with betmip and phenanthraquinone, resulted in the isolation of the known phenanthro[9,10]oxazole (**5.6**) [78JOC381], without incorporation of the amine moiety, Scheme 5.2. The 1,4,5-trisubstituted imidazoles **5.3** were characterized by their NMR spectra and elemental analyses. In the NMR spectra, the distinctive one-proton singlets for C2-H were observed at 7.60 - 7.90 ppm and their carbon signals were at 137 - 149 ppm



5.6

Scheme 5.2

Use of the unsymmetrical α-diketone, p-chlorodibenzoyl, led to the exclusive formation of 1-benzyl-4-(p-chlorophenyl)-5-phenylimidazole (**5.3c**), as confirmed by an X-ray crystallographic analysis. This corresponds to the expected initial attack of the more nucleophilic iminophosphorane nitrogen at the activated carbonyl group.

Figure 5.1 shows a perspective view and atom labelling of the crystal structure. Bond lengths and bond angles are given in Tables 5.3-4. The imidazole ring is planar with geometry comparable with that of other imidazole structures except for a slight stretching of the C(4)-C(5) bond; such stretching has been observed with similarly substituted imidazoles. The three phenyl rings are planar to within 0.01Å and their meanplanes inclined to the imidazole meanplane at angles of 82.0° (benzyl), 29.8° (4-phenyl) and 62.5° (5-phenyl). The two adjacent phenyl rings at C(4) and C(5) are mutually inclined at an angle of 58.6°. There are no unusually short (<3.4Å), intermolecular contacts between non-hydrogen atoms.

The proposed mechanism for the formation of imidazole is shown in the Scheme 5.3. Displacement of benzotriazole by a primary amine gives an N-(N′-alkylamino-

Table 5.1 Imidazoles **5.3** Prepared

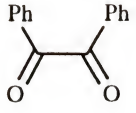
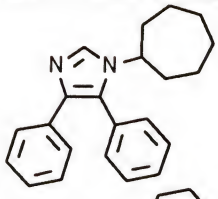
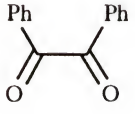
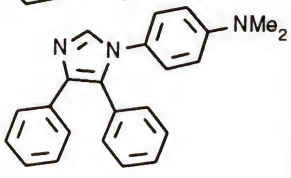
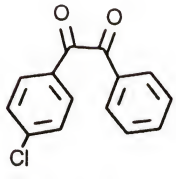
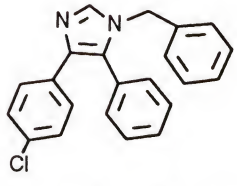
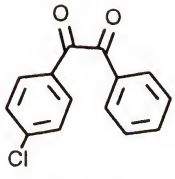
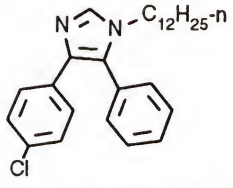
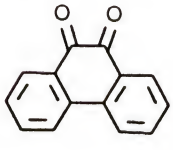
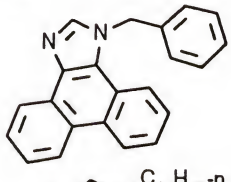
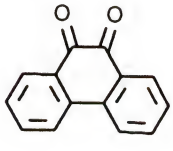
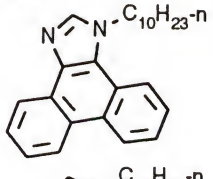
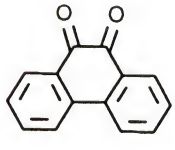
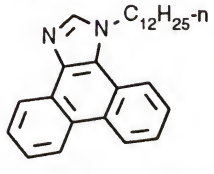
No	Amine **5.1**	α - Diketone **5.2**	Imidazole **5.3**
a	Cycloheptylamine		
b	4-Dimethylaminoaniline		
c	Benzylamine		
d	Dodecylamine		
e	Benzylamine		
f	Decylamine		
g	Dodecylamine		

Table 5.2 Preparation of 1,4,5-Trisubstituted Imidazoles **5.3**

No	Yield (%)	Molecular Formula	m.p. (°C)	C(%) Required (Found)	H(%) Required (Found)	N(%) Required (Found)
5.3a	81	$C_{22}H_{24}N_2$	132.0-133.5	83.50 (83.50)	7.64 (7.68)	8.85 (8.85)
5.3b	84	$C_{23}H_{21}N_3$	177.5-179.5	81.39 (81.43)	6.24 (6.24)	12.38 (12.49)
5.3c	55	$C_{22}H_{17}N_2Cl$	144.0-147.0	76.63 (76.83)	4.97 (4.94)	8.12 (8.00)
5.3d	53	$C_{27}H_{35}N_2Cl$	183.0-185.0	76.66 (76.30)	8.34 (8.39)	6.62 (6.47)
5.3e	79	$C_{22}H_{16}N_2$	218.0-220.0	85.69 (85.55)	5.23 (5.29)	9.08 (8.90)
5.3f	72	$C_{25}H_{30}N_2$	73.5-75.0	83.75 (83.35)	8.43 (8.63)	7.81 (7.60)
5.3g	75	$C_{27}H_{34}N_2$	75.0-77.0	83.89 (83.47)	8.87 (8.97)	7.25 (7.04)

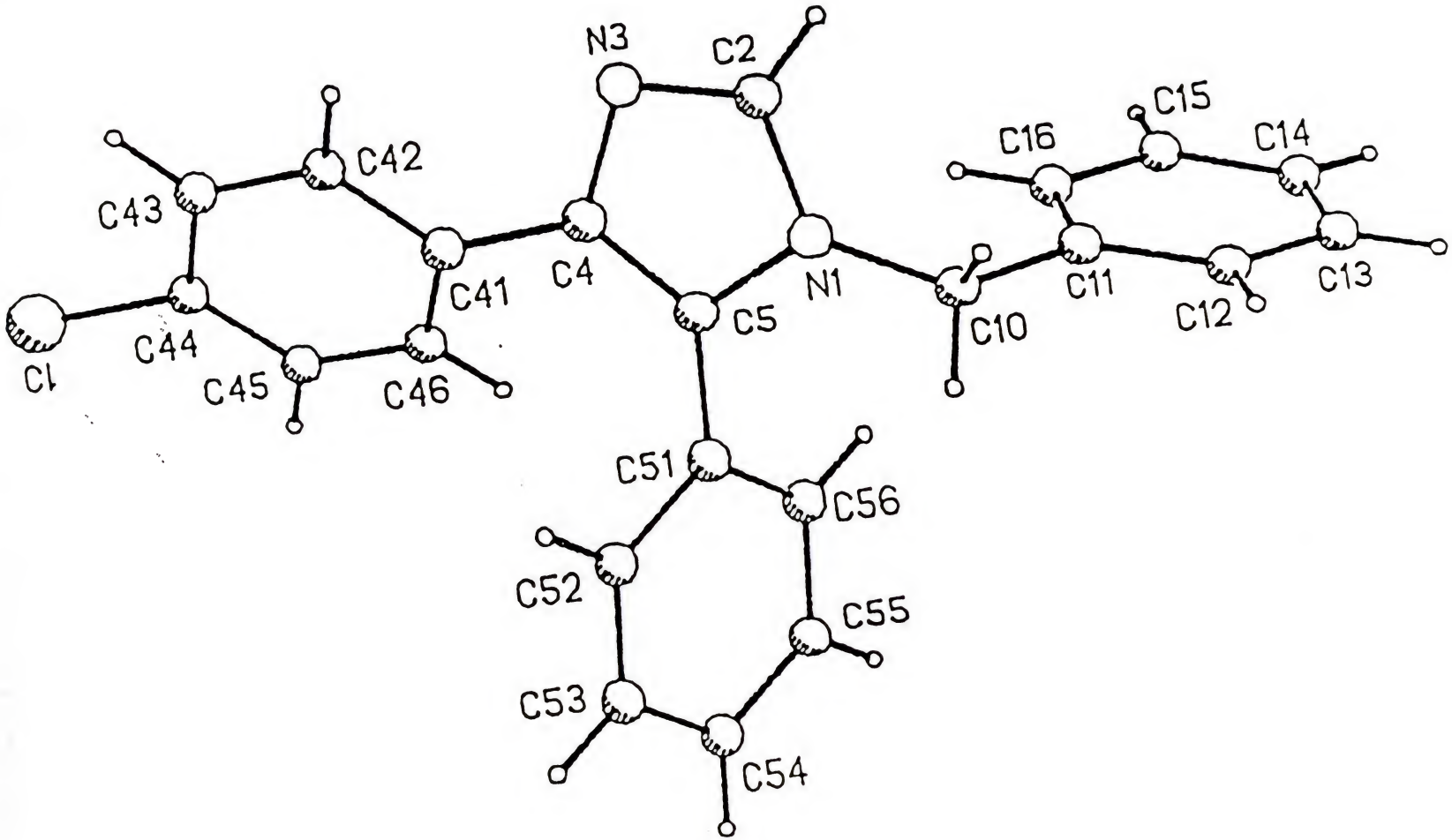
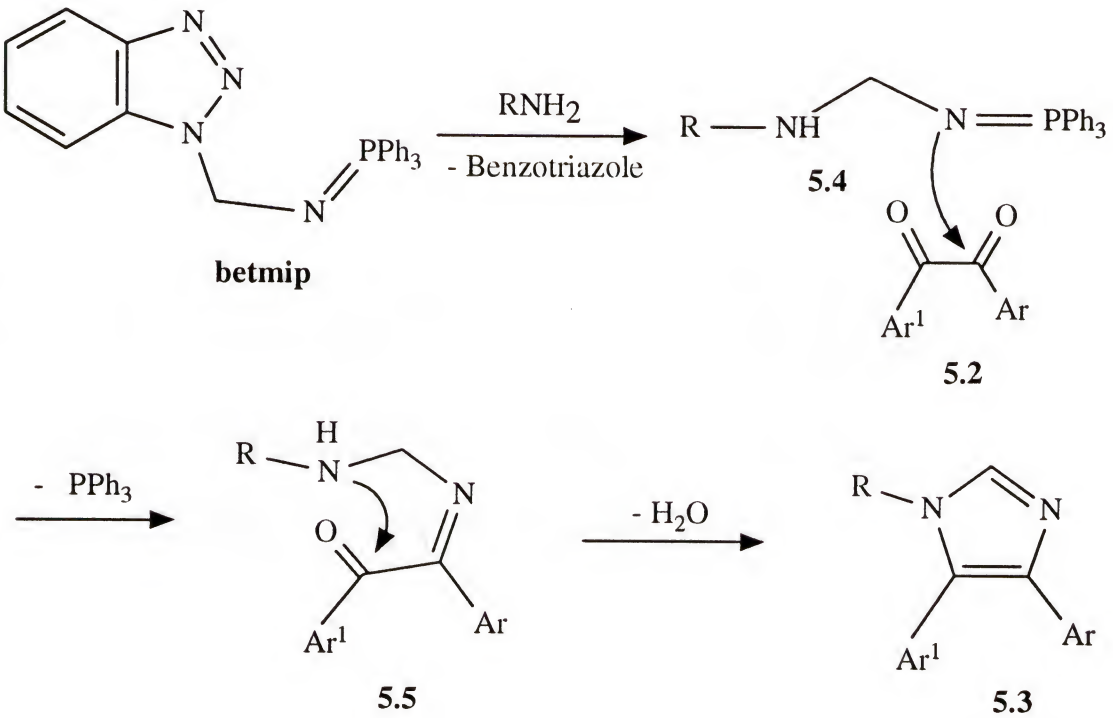


Figure 5.1 Perspective View and Atom Labeling of the X-Ray Structure of 4-(p-Chorophenyl)-5-phenylimidazole (5.3c)

methyl)iminophosphorane (**5.4**). The more reactive nucleophilic N=P group in **5.4** reacts with the more carbonyl group of the α-diketone to give the intermediate **5.5** which is dehydrated to yield the imidazole **5.3**.



Scheme 5.3 Mechanism for the Formation of 1,4,5-Trisbstituted Imidazoles **5.3**

5.3 Experimental

Column chromatography was carried out on MCB silica gel (230-400 mesh). Melting points were determined with a Kofler hot stage apparatus and were uncorrected. ^{1}H and, ^{13}C NMR spectra were recorded on a Varian VXR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal reference for ^{1}H spectra and $CDCl_3$ for ^{13}C NMR spectra (abbreviations used: s singlet, d doublet, t triplet, q quartet, qu

quintet, m multiplet, bs broad singlet and dd doublet of doublets). Elemental analyses were performed on a Carlo Erba-1106 instrument.

5.3.1 Representative Procedure for the Preparation of Imidazoles **5.3**

1-Cycloheptyl-4,5-diphenylimidazole (**5.3a**) To a solution of betmip (2.5 g, 6.1 mmol) in THF (100 ml) was added cycloheptylamine (0.69 g, 6.1 mmol). After refluxing the resulting solution for 12 hrs, benzil (1.3 g, 6.1 mmol) was added and the mixture refluxed for a further 16 hrs. The reaction mixture was cooled, diluted with diethyl ether (100 ml) and washed twice with aqueous potassium hydroxide (2 N, 25 ml) to remove the by-product benzotriazole. The crude product was column chromatographed on silica gel eluted with diethyl ether to remove triphenylphosphine oxide and some impurities to give 1-cycloheptyl-4,5-diphenylimidazole (**3.3a**) (1.57 g, 81%) as colorless needles. ^{1}H NMR 1.22-1.38 (m, 2 H), 1.49-1.60 (m, 4 H), 1.62-1.70 (m, 2 H), 1.70-1.95 (m, 2 H), 1.97-2.10 (m, 2 H), 7.05-7.22 (m, 3 H), 7.28-7.34 (m, 2 H), 7.41-7.49 (m, 5 H), 7.70 (s, 1 H); ^{13}C NMR 24.4, 27.3, 36.4, 56.4, 125.9, 126.3, 127.7, 127.8, 128.8, 129.8, 130.8, 131.0, 133.7, 134.6, 137.2.

1-(p-Dimethylaminophenyl)-4,5-diphenylimidazole (**5.3b**). ^{1}H NMR 2.90 (s, 6 H), 6.55-6.56 (d, J = 9 Hz, 2 H), 6.93-6.96 (d, J = 9 Hz, 2 H), 7.53-7.56 (d, J = 8 Hz, 2 H), 7.15-7.24 (m, 8 H), 7.70 (s, 1 H); ^{13}C NMR 40.3, 111.9, 125.1, 126.3, 126.6, 127.1, 127.7, 128.0, 128.3, 130.0, 130.4, 130.7, 134.7, 137.6, 138.2, 149.7.

1-Benzyl-4-(4-chlorophenyl)-5-phenylimidazole (**5.3c**). ^{1}H NMR 4.95 (s, 2 H), 6.93-6.98 (m, 2 H), 7.12-7.23 (m, 4 H), 7.24-7.32 (m, 3 H), 7.33-7.46 (m, 5 H), 7.63 (s, 1 H); ^{13}C NMR 48.6, 126.9, 127.7, 127.9, 128.3, 128.8, 128.9, 128.95, 129.0,130.2, 130.8, 132.0, 133.1, 136.4, 137.2, 137.3.

1-Dodecyl-4-(4-chlorophenyl)-5-phenylimidazole (**5.3d**). ^{1}H NMR 0.88 (t, J = 7

Hz, 3H), 1.2 (m, 18 H), 1.56 (qu, J = 7Hz, 2 H), 3.77 (t, J = 7 Hz, 2 H), 7.13-7.18 (m, 2 H), 7.29-7.41 (m, 2 H), 7.45-7.49 (m, 3 H), 7.59 (s, 1 H); ^{13}C NMR 14.1, 22.6, 26.4, 28.9, 29.27, 29.29, 29.4, 29.5, 29.55, 29.55, 30.7, 31.9, 127.7, 128.2, 128.7, 128.8, 129.1, 130.4, 130.6, 131.8, 133.2, 136.6, 137.0.

1-Benzylphenanthro[9,10-d]imidazole (**5.3e**). ^{1}H NMR 5.72 (s, 2 H), 7.07-7.09 (d, J = 7 Hz, 2 H), 7.23-7.28 (m, 3 H), 7.39 (t, J = 7 Hz, 1 H), 7.49 (t, J = 7 Hz, 1 H), 7.60 (t, J = 7 Hz, 1 H), 7.71 (t, J = 7 Hz, 1 H), 7.88-7.98 (m, 2 H), 8.62-8.75 (m, 3 H); ^{13}C NMR 51.2, 121.1, 122.4, 122.8, 123.1, 124.1, 124.9, 125.5, 126.0, 126.6, 127.3, 127.4, 128.0, 128.1, 129.0, 129.1, 135.8, 138.8, 140.2, 142.3.

1-Decylphenanthro[9,10-d]imidazole (**5.3f**). ^{1}H NMR 0.86 (t, J = 7 Hz, 3 H), 1.23 (m, 14 H), 1.97 (qu, J = 7 Hz, 2 H), 4.51 (t, J = 7 Hz, 2 H), 7.61 (m, 3 H), 7.70 (t, J = 7 Hz, 1 H), 7.90 (s, 1 H), 8.13 (d, J = 7 Hz, 1 H), 8.65 (d, J = 8 Hz, 1 H), 8.77 (d, J = 7 Hz, 1 H), 8.75 (m, 1 H). ^{13}C NMR 14.1, 22.6, 26.6, 29.1, 29.2, 29.40, 29.43, 30.3, 31.6, 48.1, 120.8, 122.3, 123.0, 123.3, 124.3, 124.8, 125.0, 125.3, 126.7, 127.3, 128.0, 129.0, 138.9, 141.8.

1-Dodecylphenanthro[9,10-d]imidazole (**5.3g**). ^{1}H NMR 0.88 (t, J = 7 Hz, 3 H), 1.22 (m, 18 H), 1.92 (qu, J = 7 Hz, 2 H), 4.43 (t, J = 7 Hz, 2 H), 7.56-7.62 (m, 3 H), 7.70 (t, J = 8 Hz, 1 H), 7.82 (s, 1 H), 8.09 (m, 1 H), 8.64 (d, J = 8 Hz, 1 H), 8.70 (d, J = 8 Hz, 1 H), 8.75 (m, 1 H); ^{13}C NMR 14.1, 22.6, 26.5, 29.0, 29.3, 29.37, 29.44, 29.44, 29.5, 30.2, 31.8, 48.0, 120.7, 122.3, 123.0, 123.2, 124.2, 124.8, 124.9, 125.3, 126.6, 126.2, 127.5, 127.9, 128.9, 138.7, 141.7.

5.3.2 Crystallography crystal data at -125°C (determined by Dr. Peter J. Steel)

$C_{22}H_{12}N_2Cl$, Mr = 309.4, tetragonal, space group $P4_3$, $a = b = 9.465(4)$, $c = 19.538(8)$ Å, U=1750(2) Å^3, F(000) = 720, Z = 4, $D_c = 1.31$ g cm^{-3}, $\mu(M_oK_\alpha) = 2.21$ cm^{-1}, ω-scan, $2\Theta_{max} = 60^o$, N = 2627, $N_o = 2128$, 225 parameters, S = 1.31, R = 0.046, $R_w = 0.050$. Intensity data were collected at -125°C with a Nicolet R3m four-circle diffractometer by using monochromatized M_oK_α (λ = 0.71069Å) radiation. Cell parameters were determined by least squares refinement, the setting angles of 25 accurately centered reflections ($2\Theta > 15^o$) being used. Throughout data collection the intensities of three standard reflections (008, 040, 400) were monitored at regular intervals and this indicated no significant crystal decomposition. The space groups $P4_1$ and $P4_3$ were distinguished by collecting all Friedel equivalents and merging and refining in both space groups. The intensities were corrected for Lorentz and polarization effects and for absorption by a procedure based on azimuthal φ-scans. Reflections with $I > 3\sigma(I)$ were used for structure solution and refinement.

The structure was solved by direct method, and refined by blocked cascade least-squares procedures. All non-hydrogen atoms were refined with anisotopic thermal parameters. Hydrogen atoms were included in calculated positions with isotropic thermal parameters equal to the isotropic equivalent of their carrier atoms. The function minimized was $\Sigma w(|F_o|-|F_c|)^2$, with $w = [\sigma^2(F_o)+0.00096(F_o)^2]^{-1}$. All calculations (including diagrams) were performed on a Nova 4X computer using SHELXTL. The bond lengths and bond angles are listed in Tables 5.3-4.

Table 5.3 Bond Lengths (Å)

N(1)-C(2)	1.367(4)	N(1)-C(5)	1.391(3)
N(1)-C(10)	1.464(4)	C(2)-N(3)	1.324(4)
N(3)-C(4)	1.369(4)	C(4)-C(5)	1.386(4)
C(4)-C(41)	1.478(4)	C(5)-C(51)	1.487(4)
C(10)-C(11)	1.507(4)	C(11)-C(12)	1.396(4)
C(11)-C(16)	1.392(4)	C(12)-C(13)	1.385(4)
C(13)-C(14)	1.400(5)	C(14)-C(15)	1.390(4)
C(15)-C(16)	1.393(4)	C(41)-C(42)	1.405(4)
C(41)-C(46)	1.396(4)	C(42)-C(43)	1.385(4)
C(43)-C(44)	1.390(4)	C(44)-Cl	1.743(3)
C(44)-C(45)	1.388(4)	C(45)-C(46)	1.394(4)
C(51)-C(52)	1.387(4)	C(51)-C(56)	1.386(4)
C(52)-C(53)	1.383(5)	C(53)-C(54)	1.391(5)
C(54)-C(55)	1.382(5)	C(55)-C(56)	1.394(5)

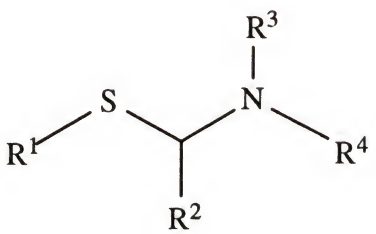
Table 5.4 Bond Angles (°)

C(2)-N(1)-C(5)	106.8(2)	C(2)-N(1)-C(10)	125.5(2)
C(5)-N(1)-C(10)	127.4(2)	N(1)-C(2)-N(3)	111.8(2)
C(2)-N(3)-C(4)	105.8(2)	N(3)-C(4)-C(5)	110.5(3)
N(3)-C(4)-C(41)	121.3(3)	C(5)-C(4)-C(41)	128.2(3)
N(1)-C(5)-C(4)	105.1(2)	N(1)-C(5)-C(51)	123.4(2)
C(4)-C(5)-C(51)	131.5(3)	N(1)-C(10)-C(11)	114.1(2)
C(10)-C(11)-C(12)	118.2(3)	C(10)-C(11)-C(16)	122.9(3)
C(12)-C(11)-C(16)	118.9(3)	C(11)-C(12)-C(13)	120.9(3)
C(12)-C(13)-C(14)	120.2(3)	C(13)-C(14)-C(15)	119.0(30
C(14)-C(15)-C(16)	120.7(3)	C(11)-C(16)-C(15)	120.4(3)
C(4)-C(41)-C(42)	118.9(3)	C(4)-C(41)-C(46)	122.7(3)
C(42)-C(41)-C(46)	118.4(3)	C(41)-C(42)-C(43)	120.8(3)
C(42)-C(43)-C(44)	119.7(3)	C(43)-C(44)-Cl	119.0(2)
C(43)-C(44)-C(45)	120.8(3)	Cl-C(44)-C(45)	120.2(2)
C(44)-C(45)-C(46)	119.1(3)	C(41)-C(46)-C(45)	121.2(3)
C(5)-C(51)-C(52)	119.6(3)	C(5)-C(51)-C(56)	120.8(3)
C(52)-C(51)-C(56)	119.5(3)	C(51)-C(52)-C(53)	120.5(3)
C(52)-C(53)-C(54)	120.1(3)	C(53)-C(54)-C(55)	119.6(3)
C(54)-C(55)-C(56)	120.3(3)	C(51)-C(56)-C(55)	120.0(3)

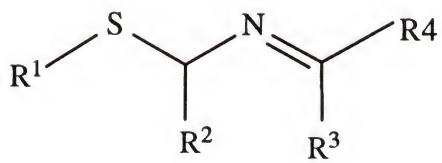
CHAPTER VI
NOVEL SYNTHESES OF FORMALDEHYDE N,S-ACETALS: N-(ALKYL-THIOMETHYL)BENZALIMINES, N-(ALKYLTHIOMETHYL)-N′-ALKYLCARBODIIMIDES, N-(ALKYLTHIOMETHYL)-N′-ALKYLUREAS AND N-(ALKYLTHIOMETHYL)AMIDES

6.1 Introduction

There has been wide interest in the development of routes to compounds containing the N-C-S unit in recent years because of the variety of natural products and biologically active derivatives in which it is included [77CPB369, 90TL3609]. In most such natural products the N-C-S moiety is part of a stable ring structure. Synthetic acyclic analogues have been studied for their pharmacological activity [90TL5345, 74JMC1225, 88TL5771]. Some analogous open chain N-C-S units also occur in synthetic intermediates frequently in the role of protective or activating groups [85JOC5260, 80CPB1942, 72TL3929, 67AP647, 82S935]. In many of the reported N-C-S derivatives **6.1**, substituent R^4 is an electron withdrawing group which confers stability, and R^2 is H. Preparative methods for derivatives **6.1** in which R^3, R^4 are alkyl include condensation of an aldehyde, a thiol and an amine [86S804], reduction of an



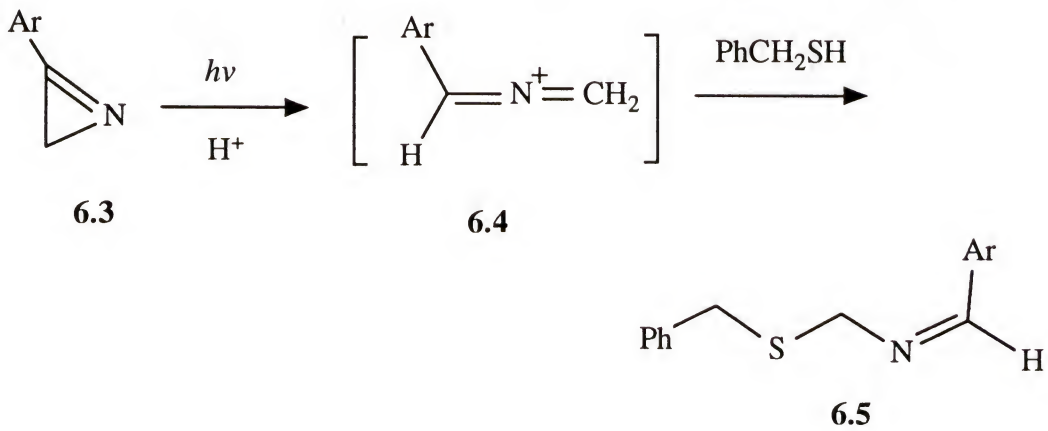
6.1



6.2

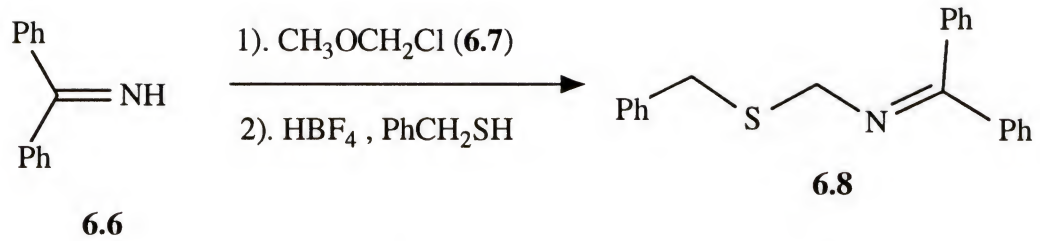
alkylthiomethyleneiminium salt with trimethoxysilane and dilithium-2,3-butandiolate [88TL5771], and substitution of the amido residue of an N-(dialkylaminomethyl)amide with a thiol [85CB4809, 73CPB2257].

In contrast to the frequent occurrence of C=N-C-S units in six membered rings (*e.g.* 1,3-(2*H*)-thiazines [83S224]) and five membered rings (*e.g.* thiazolines [58LAC121]), known C=N-C-S acyclic systems are limited to arylketimin-N,S-acetals **6.2** (R^3 = aryl and R^4 = aryl or H, R^2 = H) [78LAC381, 73CC223]. Two methods have been reported for the preparation of **6.2**. Photoconversion of arylaziridines **6.3** in the presence of benzyl thiol *via* intermediates **6.4** gave the benzyl derivatives **6.5**, Scheme 6.1 [73CC223]. The reaction of diphenylketimine **6.6** with chloromethyl methyl ether (**6.7**) followed by substitution of the methoxy group by a thiol gave the benzophenone derivative **6.8**, Scheme 6.2 [78LAC381]. The need for a photoreaction in the first example and difficulties in getting the starting materials limit both these approaches. N-Unsubstituted imines other than **6.6** in the second example spontaneously polymerized [76MI67].



6.3 **6.4** **6.5**

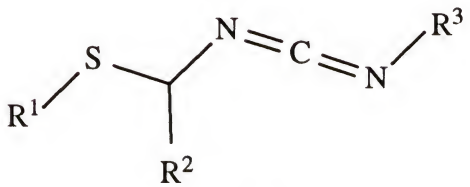
Scheme 6.1



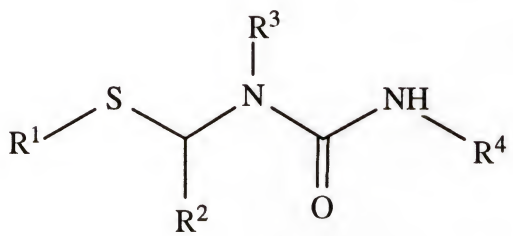
6.6 **6.8**

Scheme 6.2

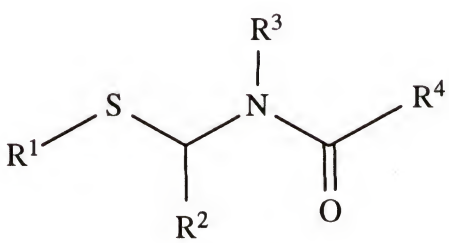
Little has been reported on carbodiimides carrying extra functional groups such as **6.9**. Tosylmethyl carbodiimides $TsCH_2N{=}C{=}NR$ have been prepared from the corresponding ureas [80JOC2070], but the literature carries no report on N-(alkylthiomethyl)carbodiimides (**6.9**). Some thiomethylureas **6.10** patented as herbicides [77USP4007033, 75USP3903154] were prepared by the addition of a thiol to the C=N bond of a Schiff base and of the resulting intermediate to an isocyanate [84EGP210902, 83EUP93610].



6.9



6.10



6.11

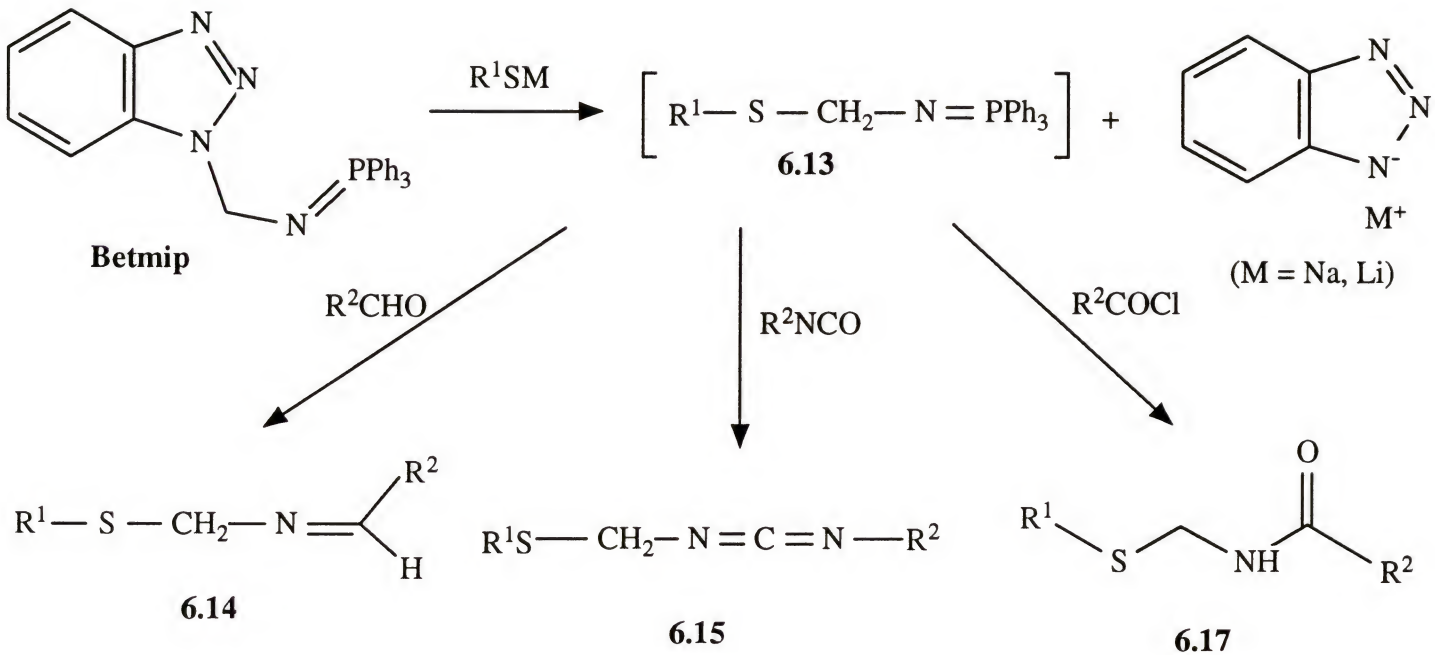
An alternative method for **6.10** only succeeded with highly activated aldehydes such as chloral [75USP3903154]. Several routes have been described for thiomethylamides **6.11**, but none is both general and convenient: several compounds **6.11** (R^3 = alkyl) were made by acylation of the appropriate N-(alkylthiomethyl)amines [81TL123]. Alternatively, an amide anion in 50% aqueous sodium hydroxide reacted with chloromethyl phenyl thioether in the presence of a phase transfer catalyst [86H1007]. Under forcing conditions, addition of acyl chloride to a Schiff base followed by the reaction with a thiol gave thiomethylamides **6.11** (R^3 = alkyl) [81CPB2496]. Few reports describe compounds **6.11** with R^3 = H: some such were prepared in aqueous solution from acetamide, formaldehyde and a water soluble thiol such as cysteine in about 50% yields [87S271, 72JA5456]. Nucleophilic substitution of the piperidine residue of N-(piperidinomethyl)benzamide with benzyl thiol gave a 23% yield of **6.11** (R^1 = $PhCH_2$, R^2 = R^3 = H, R^4 = Ph) [73CPB2257].

We now report novel one-pot syntheses from 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (betmip) of four classes of formaldehyde-N,S-acetals: N-(alkylthiomethyl)benzalimines (**6.14**), N-(alkylthiomethyl)-N′-alkylcarbodiimides (**6.15**), N-(alkylthiomethyl)-N′-alkylureas (**6.16**) and N-(alkylthiomethyl)amides (**6.17**). We have demonstrated the value of betmip as a synthon for primary amines, 1,4,5-trisubstituted imidazoles, α-(arylideneamino)alkylamines and carbodiimides, imines, isothiocyanates, aziridines and secondary amines. By analogy with the reactions of carbanions and lithium amides we anticipated that the displacement of the benzotriazole group from betmip by a thiol anion followed by reaction with an aldehyde, an isocyanate, or an acyl chloride, would provide attractive synthetic routes to derivatives with the S-CH_2N=C structural unit.

6.2 Results and Discussion

Betmip is readily available and can either be stored [90S565] or freshly prepared in THF for each reaction. The anion from 1-butanethiol was generated with sodium ethoxide in ethanol (for **6.14a**) and for other derivatives with butyllithium in tetrahydrofuran. When THF was used, the formation of the intermediate **6.13** could be monitored by the formation of a white precipitate of lithium benzotriazolate. Betmip was added to the thiolate and stirred for 10 hrs to form N-(alkylthiomethyl)iminophosphorane **6.13** as demonstrated by trapping with an aldehyde, an isocyanate, or an acyl chloride (Scheme 6.3).

Stirring the mixture of the intermediate **6.13** and the lithium salt of benzotriazole with benzaldehyde or *p*-chlorobenzaldehyde for 5 to 10 hrs at room temperature gave the required N-(alkylthiomethyl)benzalimines **6.14a-c** and **6.14d** respectively in good to excellent yields, Table 6.1. Imines **6.14a-c** could be purified by distillation, and were partially decomposed by column chromatography. However, pure **6.14d** was obtained from a silica gel column without decomposition probably because the chlorine on the phenyl ring stabilized the C=N-CH_2-S unit. Bulky substituent groups did not adversely affect the yields. The structures were supported by their elemental analyses (Table 6.2) along with the NMR spectra. The ^1H and ^{13}C NMR chemical shifts and their assignments are listed in Tables 6.3 and 6.5. The proton singlets for the formaldehyde residues were in the range 4.5 to 4.9 ppm and the carbon signals were at 57 to 61 ppm. Low field singlets (8.4 to 8.6 ppm) were observed for the CH=N protons showing that single isomers were obtained in every instance, presumably the thermodynamically more stable E isomers. The imine carbon signals showed the expected chemical shifts at 160 to 162 ppm.



Compd	R^1	M	R^2	Compd	R^1	M	R^2
6.14a	Butyl	Na	Ph	6.15b	Butyl	Li	t-Butyl
6.14b	t-Butyl	Li	Ph	6.15c	t-Butyl	Li	t-Butyl
6.14c	i-Propyl	Li	Ph	6.17a	t-Butyl	Li	Me
6.14d	t-Butyl	Li	4-Cl-Ph	6.17b	t-Butyl	Li	Ph
6.15a	i-Propyl	Li	t-Butyl				

Scheme 6.3

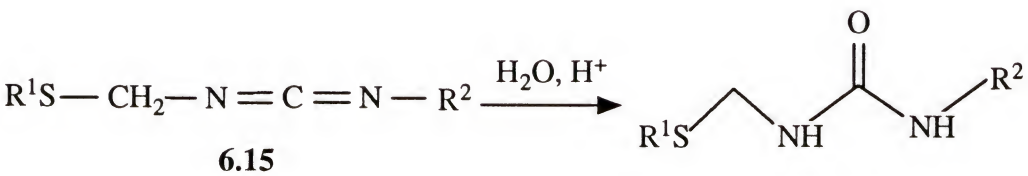
Table 6.1 Preparation of N-(Alkylthiomethyl)benzalimines (**6.14**) N-(Alkylthiomethyl)-N′-alkylcarbodiimides (**6.15**), N-(Alkylthiomethyl)-N′-alkylureas (**6.16**) and N-(Alkylthiomethyl)amides (**6.17**)

Compound	Yield (%)	b.p. (^{o}C/mmHg) or m.p. (^{o}C)	Purification Solvent
6.14a	74	125-128 / 1	Distillation
6.14b	76	115-118 / 1	Distillation
6.14c	85	110-112 / 1	Distillation
6.14d	85	oil	Et_2O
6.15a	83	78-81 / 1	Distillation
6.15b	80	83-86 / 0.5	Distillation
6.15 c	85	89-92 / 0.5	Distillation
6.16a	92	117 - 118	Hexane
6.16b	90	92.5 - 93.5	Hexane
6.16c	87	94.5 - 93.5	Hexane
6.17a	82	41.5 - 43	Hexane
6.17b	75	84 - 85	Hexane / Et_2O

Table 6.2 CHN Analyses of N-(Alkylthiomethyl)benzalimines (**6.14**) N-(Alkylthiomethyl)-N′-alkylcarbodiimides (**6.15**) N-(Alkylthiomethyl)-N′-alkylureas (**6.16**) and N-(Alkylthiomethyl)amides (**6.17**)

Compd	Formula	CHN Analysis, Found (reqired)		
		C%	H%	N%
6.14a	$C_{12}H_{17}NS$	69.35 (69.52)	8.30 (8.26)	6.70 (6.76)
6.14b	$C_{12}H_{17}NS$	69.27 (69.52)	8.34 (8.26)	6.66 (6.76)
6.14c	$C_{11}H_{15}NS$	68.45 (68.35)	7.89 (7.82)	7.12 (7.25)
6.14d	$C_{12}H_{16}NSCl$	59.83 (59.61)	6.72 (6.67)	5.73 (5.79)
6.15a	$C_9H_{18}N_2S$	58.11 (58.02)	9.77 (9.74)	14.96 (15.04)
6.15b	$C_{10}H_{20}N_2S$	59.44 (59.45)	10.18 (10.06)	13.89 (13.98)
6.15 c	$C_{10}H_{20}N_2S$	60.03 (59.95)	10.09 (10.06)	13.90 (13.95)
6.16a	$C_9H_{20}N_2OS$	52.99 (52.90)	10.01 (9.87)	13.77 (13.71)
6.16b	$C_{10}H_{22}N_2OS$	54.84 (55.01)	10.19 (10.16)	13.18 (12.83)
6.16c	$C_{10}H_{22}N_2OS$	55.02 (55.01)	10.38 (10.16)	12.91 (12.83)
6.17a	$C_7H_{15}NOS$	51.98 (52.15)	9.29 (9.38)	8.72 (8.69)
6.17b	$C_{12}H_{17}NOS$	64.52 (64.54)	7.64 (7.68)	6.57 (6.28)

N-(Alkylthiomethyl)-N′-t-butylcarbodiimides (**6.15**) were prepared in good yields *via* the intermediate **6.13** by stirring with t-butyl isocyanate in THF at room temperature. Phenyl isocyanate failed to form satisfactory products and the NMR spectra were so complex that no conclusions about the reactions could be reached. Presumably the steric hindrance imposed by the t-butyl group in t-butyl isocyanate is an advantage in limiting side reactions and giving almost exclusive formation of the required carbodiimides. The carbodiimides **6.15** obtained by distillation are stable in water and in a basic aqueous suspension, thus all N-(alkylthiomethyl)-N′-alkylcarbodiimides (**6.15**) were recovered after stirring in H_2O-THF or 0.1 N NaOH-THF at room temperature for 3 days. In 0.01 N hydrochloric acid, N-(alkylthiomethyl)-N′-alkylcarbodiimides (**6.15**) gave N-(alkylthiomethyl)-N′-alkylureas (**6.16**) in quantitative yields.



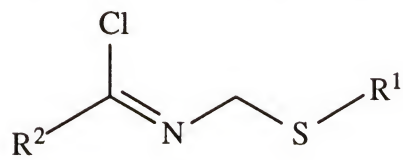
6.15 **6.16**

Compd	R^1	R^2
6.16a	i-Propyl	t-Butyl
6.16b	t-Butyl	t-Butyl
6.16c	Butyl	t-Butyl

Scheme 6.4

The structures of both carbodiimides **6.15** and ureas **6.16** were established by elemental analyses and NMR data (Tables 6.3-6.6). Low intensity carbon signals at about 140 ppm were as expected for the carbodiimide system of **6.15.** The carbonyl groups in the ureas **6.16** were observed at 156 to 157 ppm. The typical downfield triplets at about 5.7 ppm for the NH groups in **6.16a** and **6.16c** and 4.8 ppm in **6.16b** coupled with the CH_2 groups (formaldehyde residues) in the ^1H NMR spectra, while the singlets at about 5.2 ppm for **6.16a** and **6.16c**, and 4.68 ppm for **6.16b** are for the other NH groups

When the suspension containing intermediate **6.13** was treated with acetyl chloride or benzoyl chloride at room temperature, high yields of N-(alkylthiomethyl)amides (**6.17a** and **6.17b**) were obtained. The amides **6.17** formed were not decomposed during basic aqueous work-up and pure products were conveniently obtained through a short chromatography column. The mechanism for the



6.18

formation of amides **6.17** is probably *via* the intermediates **6.18** [81T437] with the oxygen atom of the carbonyl group derived from H_2O during aqueous work-up.

In conclusion, betmip has provided the first N-(alkylthio-methyl)iminophosphoranes (**6.13**) which were conveniently transformed, without isolation and in high yields, into diverse compounds with acyclic N-C-S systems as exemplified by the novel imines **6.14**, carbodiimides **6.15**, ureas **6.16** and amides **6.17**.

Table 6.3 ^{1}H NMR of $R^1SCH_2N{=}CHR^2$ (**6.14**) and $R^1SCH_2N{=}C{=}CR^2$ (**6.15**)

Compd	R^1	SCH_2- (S, 2 H)	CH= (S, 1 H)	R^2
6.14a	1.38 (3 H, t, J = 7 Hz, CH_3) 1.56 (2 H, m, CH_2) 1.60 (2 H, m, CH_2) 2.52 (2 H, t, J = 7 Hz)	4.74	8.41	7.40 (3 H, m) 7.81 (2 H, m)
6.14b	1.38 (9 H, s, CH_3)	4.85	8.45	7.38 (3 H, m) 7.75 (2 H, m)
6.14c	1.17 (6 H, d, J = 7 Hz, CH_3) 2.85 (1 H, m, CH)	4.68	8.35	7.27 (3 H, m) 7.76 (2 H, m)
6.14d	1.39 (9 H, s, CH_3)	4.85	8.50	7.37 (2 H, d, J = 9 Hz)) 7.68 (2H, d, J = 9 Hz)
6.15a	1.34 (6 H, d, J = 7 Hz, CH_3) 3.18 (1 H, m, J = 7 Hz, CH)	4.22	----	1.35 (9 H, s, CH_3)
6.15b	0.95 (3 H, t, J = 7 Hz, CH_3) 1.42 (2 H, m, CH_2) 1.63 (2 H, m, CH_2) 2.70 (2 H, t, J = 7 Hz, CH_2)	4.22	----	1.33 (9 H, s, CH_3)
6.15c	1.38 (9 H, s, CH_3)	4.26	----	1.32 (9 H, s, CH_3)

Notes: Solution in $CDCl_3$; chemical shifts in ppm; coupling constants J (in brackets) in Hz.

Table 6.4 ^1H NMR of $R^1SCH_2NHC(O)NHR^2$ (**6.16**) and $R^1SCH_2NHC(O)R^2$ (**6.17**)

Compd	R^1	SCH_2 (2 H, J = 6.0 Hz)	NH	R^2
6.16a	1.30 (6 H, d, J = 7.0 Hz, CH_3) 3.08 (1 H, h, J = 7.0 Hz, CH)	4.35	5.27 (1 H, s) 5.75 (1 H, t, J = 6.0 Hz)	1.35 (9 H, s, CH_3)
6.16b	1.36 (9 H, s, CH_3)	4.38	4.68 (1 H, s) 4.83 (1 H, t, J = 6.0 Hz)	1.33 (9 H, s, CH_3)
6.16c	0.91 (3 H, t, J = 7.0 Hz, CH_3) 1.58 (2 H, m, CH_2) 2.60 (2 H, m, CH_2)	4.31	5.18 (1 H, s) 5.65 (1 H, t, J = 6.0 Hz)	1.33 (9 H, s, CH_3)
6.17a	1.37 (9 H, s, CH_3)	4.43	6.78 (1 H, b)	2.10 (3 H, s, CH_3)
6.17b,	1.38 (9 H, s, CH_3)	4.63	6.92 (1 H, b)	7.35-7.55 (3 H, m) 7.80 (2 H, J = 8.5 Hz)

Notes: Solution in $CDCl_3$; chemical shifts in ppm from TMS; coupling constants J (in brackets) in Hz.

Table 6.5 ^{13}C NMR of $R^1SCH_2N=CHR^2$ (**6.14**) and $R^1CH_2SN=C=NR^2$ (**6.15**)

Compd	R^1	SCH_2-	C=N	R^2
6.14a	13.66, 21.93, 30.69, 31.61	60.57	161.62	135.66, 130.93, 128.58, 128.40
6.14b	31.42, 43.23	57.47	161.67	135.67, 130.62, 128.37, 128.10
6.14c	23.56, 34.21	59.27	161.62	135.73, 130.92, 128.58, 128.40
6.14d	31.45, 43.42	57.46	160.41	136.65, 134.21, 129.36, 128.74
6.15a	23.00, 34.25	55.53	139.64	31.15, 46.91
6.15b	13.53, 21.86, 31.36, 48.40	55.76	139.65	31.22, 48.40
6.15c	31.19, 43.01	55.65	140.15	31.30, 45.81

Notes: Solution in $CDCl_3$; chemical shifts in ppm from TMS

Table 6.6 ^{13}C NMR of $R^1SCH_2NHC(O)NHR^2$ (**6.16**) and $R^1SCH_2NHC(O)NHR^2$ (**6.17**)

Compd	R^1	SCH_2	C=O	R^2
6.16a	23. 69, 41.53	50.25	157.33	34.11, 41.53
6.16b	29.32, 40.30	50.52	156.52	31.32, 43.30
6.16c	13.60, 21.99 30.30, 31.83	50.26	157.30	29.42, 42.56
6.17a	30.86, 38.46	42.84	169.87	22.86
6.17b	31.09, 39.31	43.23	166.69	126.80, 128.36, 131.42, 133.95

Notes: Solution in $CDCl_3$; chemical shifts in ppm from TMS

6.3 Experimental

Melting points were measured with a Kofler hot Stage apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on either a Varian VXR-300 or a General Electric QE-300 (FT-mode) spectrometer at 300 MHz and 75 MHz respectively in $CDCl_3$. TMS was used as an internal reference for the ^{1}H NMR spectra. Elemental analyses were performed in house or at Atlantic Microlab Inc. THF was freshly distilled from sodium-benzophenone ketyl immediately before use.

6.3.1 General Procedures for the Preparation of N-(Alkylthiomethyl)benzalimines (**6.14**)(Method A)

N-(Butylthiomethyl)benzalimine (**6.14a**). 1-Butanethiol (2.14 g, 23.7 mmol) in absolute ethanol (80 ml) was stirred with sodium (0.57 g, 24.2 mmol) until the metal was dissolved . Betmip (6.0 g, 15.0 mmol) in absolute ethanol (40 ml) was added to the solution and stirred for 10 hrs at room temperature. Benzaldehyde (1.56 g, 15.0 mmol) in absolute ethanol (10 ml) was added and stirring continued for 5 hrs further. The solvent was removed under vacuum and the residue vigorously shaken with diethyl ether (100 ml). The solid was filtered off, washed with diethyl ether (3 x 15 ml), the filtrate dried ($MgSO_4$) and the solvent evaporated to give an oily residue. Distillation gave 2.25 g (74%) of essentially pure product. ^{1}H NMR 1.38 (3 H, t, J = 7 Hz), 1.56 (2 H, m), 1.60 (2 H, m), 2.52 (2 H, t, J = 7 Hz), 4.74 (2 H, s), 7.40 (3 H, m), 7.81 (2 H, m), 8.41 (1 H, s); ^{13}C NMR 13.66, 21.93, 30.69, 31.61, 60.57, 128.40, 128.58, 130.93, 135.66, 161.62.

6.3.2 General procedure for the preparation of N-(alkylthiomethyl)benzalimines (**6.14**), N-(alkylthiomethyl)-N′-alkylcarbodiimides (**6.15**) and N-(alkylthiomethyl)amides (**6.17**) (Method B)

Butyllithium (8.5 ml, 2.5 M solution in hexane, 21 mmol) was added to a solution of t-butanethiol (1.95 g, 21 mmol) in THF (80 ml) under argon at -78°C. The cooling bath was removed and the mixture stirred until a clear solution formed (15 min). This was stirred with betmip (7.8 g, 21 mmol) for 10 hrs at room temperature followed by one molar equivalent (21 mmol) of the appropriate reagent either an aldehyde, or an isocyanate, or an acyl chloride for another 10 hrs at room temperature. The reaction for N-(alkylthiomethyl)benzalimines (**6.14**) and N-(alkylthiomethyl)-N′-alkylcarbodiimides (**6.15**) was worked up as described above. The mixture containing **6.17** was quenched with water (30 ml) and extracted with diethyl ether (2 x 60 ml). The organic layer was washed with 3N NaOH (2 x 30 ml), dried ($MgSO_4$) and the solvent removed. The amides (**6.17**) were obtained by column chromatography (silica gel, diethyl ether-hexane (1 : 1)) and were recrystallized from hexane-ethyl acetate.

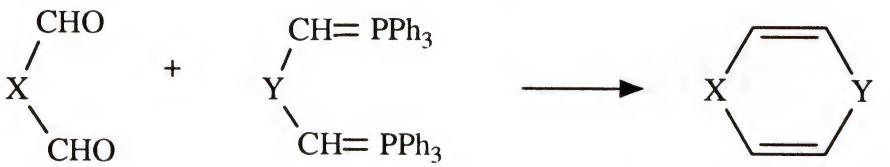
6.3.2 General Procedures for the Preparation of N-(Alkylthiomethyl)-N′-alkylureas (**6.16**)

Carbodiimide **6.15a** (0.5 g, 2.5 mmol) in 0.01N HCl-THF (1:1, 5 ml) was stirred 1 hr at room temperature. The mixture was extracted with ethyl acetate (2 x 5 ml). The organic layer was dried ($MgSO_4$) and the solvent removed to give a white solid **6.16a** (0.49 g, 92%) which was recrystallized from diethyl ether-hexane.

CHAPTER VII
BETMIP, APPLICATION TO SYNTHESIS OF NOVEL 1,2- AND 1,3-MONOAZABISYLIDES

7.1 Introduction

The conversion of an aldehyde or ketone into an alkene can be achieved by the Wittig reaction. The same type of reaction of an iminophosphorane with a carbonyl group (an aza-Wittig) gives an imine. Both reactions are extremely important in organic synthesis, as can be judged from the amount of review literature that has been published [65OR270] [64PAC245] [81T437] [92T1353] [92OPP209]. One application of particular importance is the preparation of cyclic olefins by bis Wittig reactions, *i.e.* a double intermolecular processes between one mol of a dicarbonyl compound **7.1** and one mol of a bis-alkylidenetriphenylphosphorane **7.2** (a bis-ylide) which lead to the unsaturated cyclic compound **7.3** (Scheme 7.1).



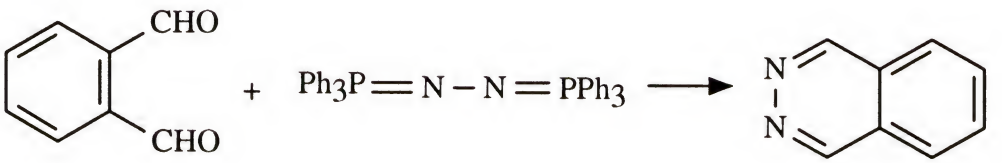
7.1 **7.2** **7.3**

Scheme 7.1

This method for the preparation of cyclic olefins offers a number advantages over other synthetic procedures particularly in the cases of large rings. The unsaturated rings synthesized range in size from five membered to thirty six membered [75S765].

A bis-aza-Wittig reaction has been reported for the preparation of

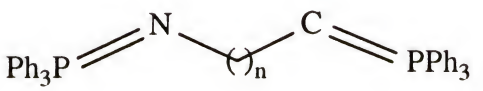
benzopyrimidine **7.6** from the azabisylide (triphenylphosphine-azine, **7.5**) and phthalic dicarboxaldehyde **7.4** [68ZAC(363)183] (Scheme 7.2). However, monoazabisylides,



7.4 **7.5** **7.6**

Scheme 7.2

which should be useful in the synthesis of heterocycles, have seldom been reported [89TL5493] and the monoazabisylides (**7.7** with n = 0, 1) are unknown.



7.7

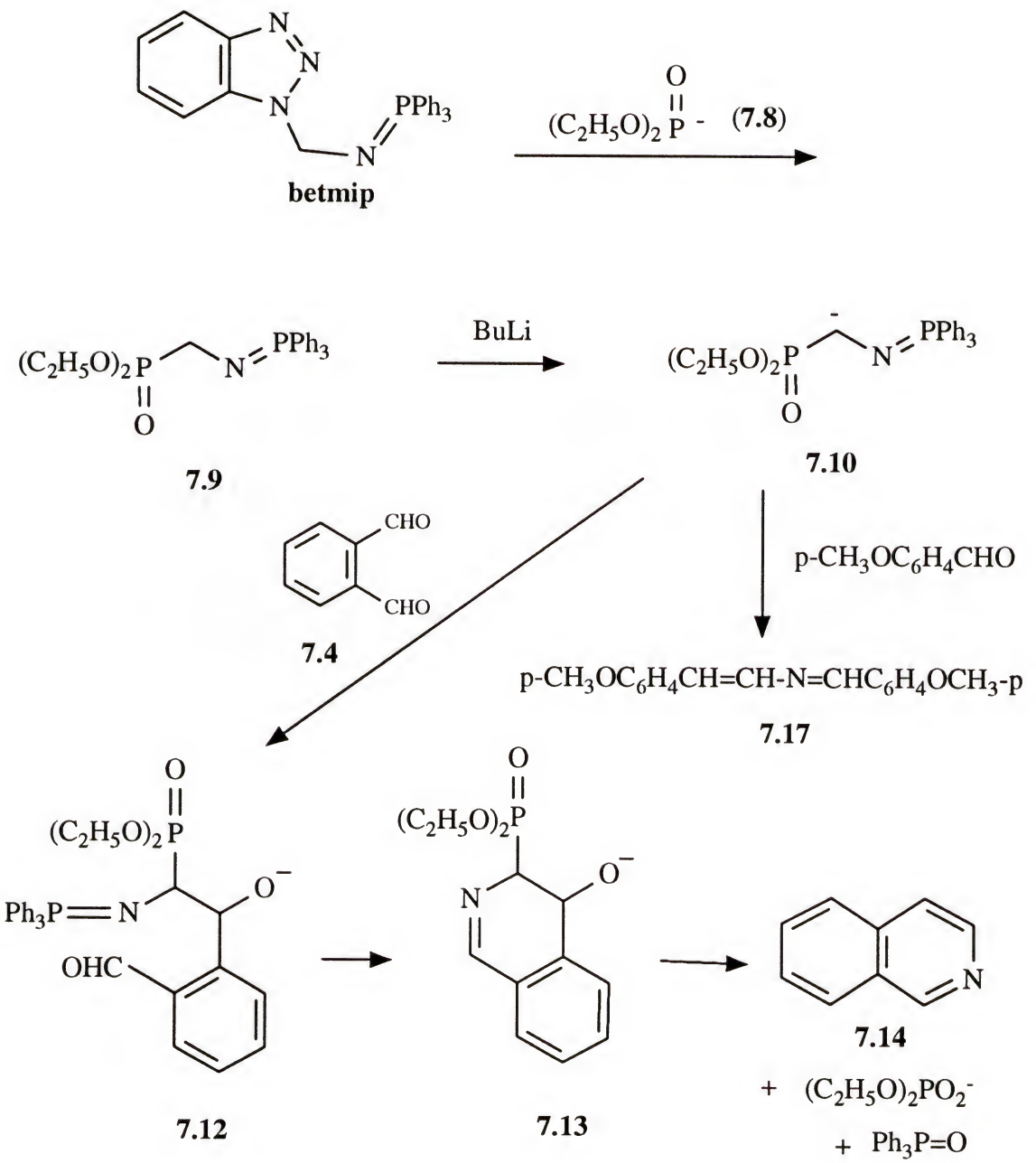
1-(Triphenylphosphoroylideneaminomethyl)benzotriazole (betmip) has demonstrated usefulness in novel syntheses of primary amines, 1,4,5-trisubstituted imidazoles and in the preparation of carbodiimides, imines, isothiocyanates, aziridines, secondary amines α-(arylideneamino)alkylamines and formaldehyde-N,S-acetals. Here we report the synthesis of 1,2- **7.10** and 1,3-monoazabisylides **7.22** and their use in the synthesis of isoquinoline **7.14**, 2-azabutadienes **7.17**, 4-aza-1,8-diphenyl-1,3,5,7-octatetrene (**7.19**), 2,3-diarylpyrroles **7.27** and 2-(*3H*)-benzazepines (**7.24**).

7.2 Results and Discussion

As reported in the previous chapters, benzotriazole in betmip can readily be displaced by nucleophiles such as carbanions [89TL3303] and lithium amides. 1,2-monoazabisylide **7.10** was prepared from a reaction of betmip and diethyl phosphite anion **7.8** (prepared *in situ* by stirring diethyl phosphite with butyllithium at room temperature). The formation of intermediate **7.9** was monitored by the precipitation of the lithium salt of benzotriazole and the resulting suspension was treated with butyllithium at - 78°C. A change of color from black to yellow when the temperature rose to room temperature indicated that the deprotonation was complete to give **7.10**. Treatment with phthalic dicarboxaldehyde (**7.4**) then gave isoquinoline **7.14** in 55% yield, as confirmed by the ^{1}H and ^{13}C NMR spectra compared with those reported in the literature [66AJC187] [69JA638]. Similarly, p-anisaldehyde gave 1,4-di(4-methoxylphenyl)-2-azabutadiene (**7.17c**) in a yield of 60%.

It was reported that the elimination of diethyl phosphate anion in the Horner-Emmons reaction needs an electron-withdrawing group at the carbon adjacent to the phosphorus atom. The mechanism for the reaction of the 1,2-monoazabisylide with phthalic dicarboxaldehyde (**7.4**) is probably the formation of a σ-bond at the carbon end of the 1,2-monoazabisylide **7.10** to give **7.12** followed by ring closure with the formation of the C=N bond to give **7.13**, and finally the elimination of diethyl phosphate anion to give isoquinoline **7.14**.

Without initial reaction with butyllithium, intermediate **7.9** reacted with aryl aldehydes to give 2-azabutadienes **7.17a-d** and reacted with cinnamaldehyde (**7.18**) to

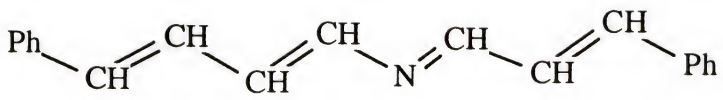

betmip
(7.8)
BuLi
7.9
7.10
7.4
p-CH3OC6H4CHO
p-CH3OC6H4CH=CH-N=CHC6H4OCH3-p
7.17
7.12
7.13
7.14
+ (C2H5O)2PO2-
+ Ph3P=O

Scheme 7.3

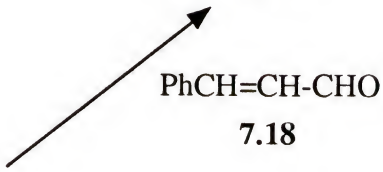
give 4-aza-1,8-diphenyl-1,3,5,7-octatetrene (**7.19**) in good yields (75-86%). This is also a stepwise aza-Wittig-Horner-Emmons reaction. The aza-Wittig reaction of intermediate **7.9** with one molecule of an aldehyde gave **7.15**. One proton on the methylene group of **7.15**, bearing two electron-withdrawing groups, was deprotonated by another molecule of **7.9** to give carbanion **7.16**. Finally the Horner-Emmons reaction with a second molecule of the aldehyde gave 2-azabutadienes **7.17**. Compounds **7.17a-e** were characterized by ^{1}H and ^{13}C NMR, and the new compounds **17b-e** were supported by CHN analyses. All products showed sharp singlets for the CH=N protons which indicate single configurations.

The 1,3-monoazabisylide **7.22** was prepared similarly. Reaction of betmip with methylenetriphenylphosphorane for 10 hrs at room temperature gave the solid phosphonium salt **7.21** in THF which was then treated with butyllithium at - 78°C to give a suspension of **7.22**. After stirring with phthalic dicarboxaldehye (**7.4**) at room temperature, the suspension changed to a deep purple solution, and 2-(*3H*)-benzazepine (**7.24**) was isolated in 62% yield. 2,3-Diphenylpyrrole (**7.27a**), 2,3-di-(4-methylphenyl)pyrrole (**7.27b**) and 2,3-dipyrid-2-ylpyrrole (**7.27c**) were prepared similarly from benzil (67%), 4,4′-dimethylbenzil (75%) and 2,2′-dipridil (58%) respectively. The mechanism for the reaction of the 1,3-monoazabisylide with dicarbonyl compounds is probably stepwise. The more reactive carbon ylide in **7.22** reacts with one carbonyl group to give the predominant Z-alkenes **7.23** first, then the aza-Wittig reaction forms the C=N bond to complete the cyclization.

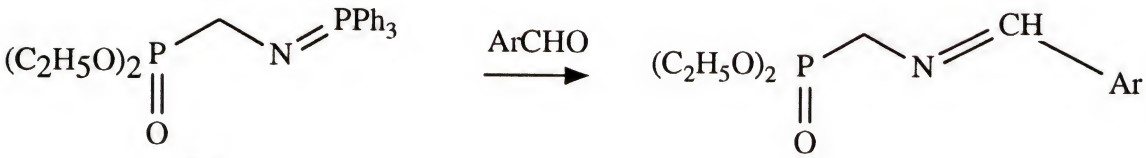
2,3-Disubstituted pyrroles (**7.27**) and 2-(*3H*)-benzazepine (**7.24**) were characterized by ^{1}H and ^{13}C NMR and confirmed by CHN analyses or H.R.M.S. The two pyrrole ring proton signals of **7.27** appeared at 6.20-6.40 ppm and 6.50-6.80 ppm respectively in the ^{1}H NMR spectra. The characteristic C-5 carbon signals of the



7.19

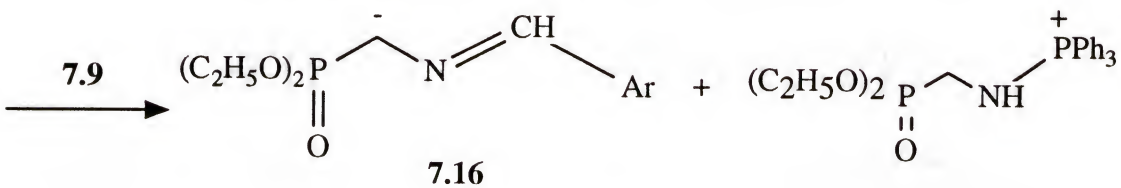


7.18

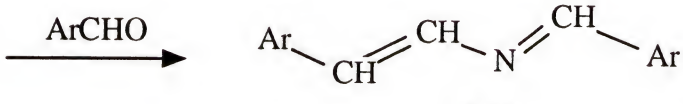


7.9

7.15

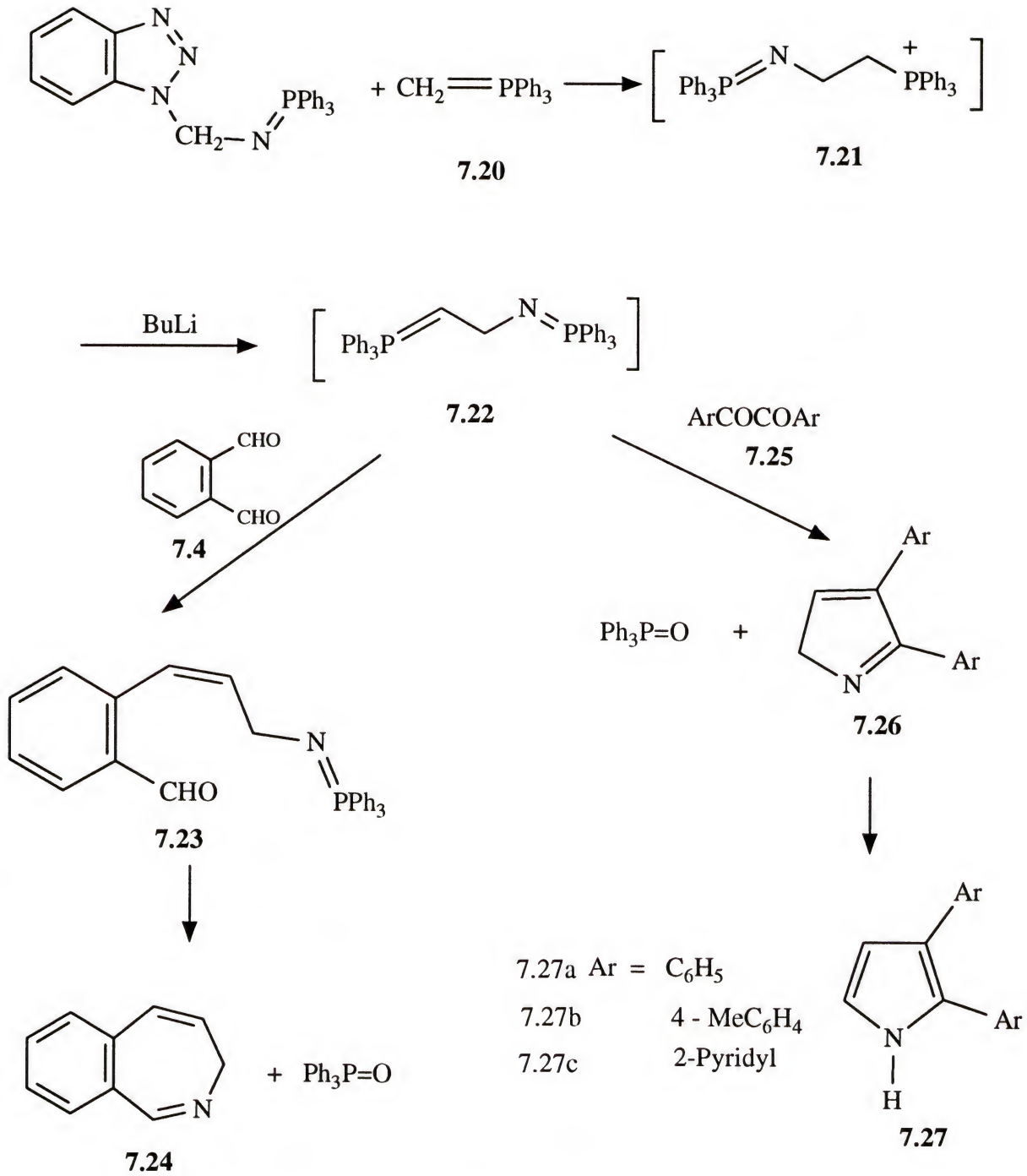


7.16



7.17

7.17a	Ar =	C_6H_5
7.17b		p-Cl-C_6H_4
7.17c		p-F-C_6H_4
7.17d		p-CH_3O-C_6H_4


+ CH2=PPh3
7.20
7.21
BuLi
7.22
ArCOCOAr
7.25
7.4
CHO
CHO
Ph3P=O +
7.26
7.23
CHO
PPh3
7.24
+ Ph3P=O
7.27a Ar = C6H5
7.27b 4 - MeC6H4
7.27c 2-Pyridyl
7.27

Scheme 7.5

Table 7.1 Preparation of **7.14, 7.17, 7.19, 7.24, 7.27 .**

No	Yield (%)	m.p. (°C) or b.p. (°C/mmHg)	Formula	Lit. m.p. or b.p. or CHN Analysis or HRMS, Found (Required) C% H% N%
7.14	55	82-85 / 1	C_9H_7N	243 °C(b.p.) [79MI(4)214]
7.17a	76	53 -55	$C_{15}H_{13}N$	51 - 53 °C (m.p.) [90JOC2878]
7.17b	85	192 -193	$C_{15}H_{11}NCl_2$	65.54 (65.24), 4.03 (4.01), 5.07 (5.07)
7.17c	86	123 -124	$C_{15}H_{11}NF_2$	74.23 (74.06), 4.58 (4.56), 5.79 (5.76)
7.17d	65	178 -179	$C_{17}H_{17}NO_2$	76.20 (76.38), 6.41 (6.41), 5.41 (5.24)
7.19	70	143 -145	$C_{19}H_{17}N$	87.30 (87.69), 6.57 (6.76), 5.31 (5.55)
7.24	62	89 - 92 / 0.5	$C_{10}H_9N$	143.0731 (143.0735)
7.27a	67	128 - 129 [a]	$C_{16}H_{13}N$	87.64 (87.28), 5.98 (6.01), 6.39 (6.24)
7.27b	75	124 - 125	$C_{18}H_{17}N$	87.39 (87.41), 7.10 (6.93), 5.34 (5.66)
7.27c	58	oil	$C_{14}H_{11}N_3$	76.01 (76.00), 5.16 (5.01), 18.85 (18.99)

a. Lit. m.p. 130 - 131°C [86BCJ1809] .

pyrrole ring were observed at 111-112 ppm. The NH protons of **7.27a** and **7.27b** were

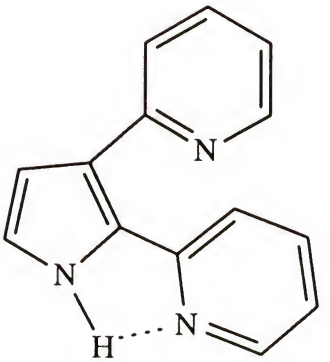


Fig . 7.1

at 8.10-8.15 ppm, and about 11.10 ppm for **7.27c**, obviously because of the intramolecular hydrogen bond, Fig 7.1. The new 2-(*3H*)-benzazepine (**7.24**) gave the expected NMR spectra. The methylene protons appeared as a doublet at 3.67 ppm (J = 9 Hz). The proton on the carbon adjacent to the methylene group showed a multiplet at 5.95 ppm. The sharp singlet at 8.27 ppm was reasonable for the CH=N proton. The final proton in the seven membered ring is a doublet at 6.65 ppm (J = 10 Hz).

In summary, these results have introduced new and convenient synthons for heterocyclic synthesis. The 1,2-monoazabisylide offers a new route to isoquinoline synthesis. The 1,3-monoazabisylide represents the first synthon for the conversion of α-diketones to 2,3-disubstituted pyrroles, and has enabled the first preparation of unsubstituted 2-(*3H*)-benzazepine.

7.3 Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 MHz spectrometer in $CDCl_3$. THF was freshly distilled from sodium-benzophenone ketyl immediately before use.

7.3.1 Preparation of 1,2-Monoazabisylide **7.10** and Isoquinoline **7.14**

Butyllithium (6.0 ml, 15.0 mmol, 2.5 M solution in hexane) was added to a solution of diethyl phosphite (2.0 g, 14.0 mmol) in THF (40 ml) under argon at -78°C. The cooling bath was removed and the reaction mixture was stirred for 0.5 hr. This was stirred with betmip (5.9 g, 14.0 mmol) at room temperature overnight until no more precipitate was formed. Butyllithium (6.0 ml, 15.0 mmol, 2.5 M solution in hexane) was added at -78°C and stirring continued at -78°C for 2 hrs and at room temperature a further 0.5 hr. The mixture was stirred with phthalic dicarboxaldehyde (1.75 g, 13.0 mmol) for 2 hrs at -78°C then overnight at room temperature. The reaction was quenched with water (40 ml) and extracted with diethyl ether (3 x 40 ml). The combined organic layer was washed with 3 N NaOH (2 x 30 ml). The solvent was removed, the residue dissolved in $CHCl_3$ (40 ml) and extracted with 2 N HCl (2 x 30 ml). The aqueous solution was made basic with 3N NaOH and extracted with $CHCl_3$ (2 x 30 ml). The organic layer was dried with $MgSO_4$ and the solvent removed to give isoquinoline **7.14** (0.95 g, 55%). ^{1}H NMR 7.40-7.60 (3H, m), 7.75 (1 H, d, J = 8 Hz), 7.80 (1 H, d, J = 8 Hz), 8.50 (1 H, d, J = 6 Hz), 9.2 (1 H, s); ^{13}C NMR 119.68, 125.66, 126.44, 126.76, 127.88, 129.52, 134.91, 142.25, 151.75; identical in all respects with the spectra reported in the literature [79MI(4)214]

7.3.2 Representative Procedure for the Preparation of 1,4-Diaryl-2-azabutadienes **7.17** and 1,8-Diphenyl-4-azaoctatetraene (**7.19**)

1,4-Diphenyl-2-azabutadiene (**7.17a**). Butyllithium (6.0 ml, 15.0 mmol, 2.5 M solution in hexane) was added to a solution of diethyl phosphite (2.0 g, 14.0 mmol) in THF (40 ml) under argon at -78°C. The cooling bath was removed and the mixture was stirred for 15 min. This was stirred with betmip (5.9 g, 14.0 mmol) overnight. Benzaldehyde (1.5 g, 14.0 mmol) in THF (15 ml) was added and stirring continued for another 10 hrs. The solvent was removed under vacuum and the residue vigorously shaken with ethyl acetate (15 ml), then diluted with diethyl ether (60 ml). The solid was filtered off and washed with diethyl ether (3 x 15 ml). The filtrate was dried ($MgSO_4$) and the solvent removed to give a solid residue which was purified through a short column (silica gel - diethyl ether) (1.1 g, 76% yield) and recrystallized from hexane. ^{1}H NMR 7.05 (1 H, d, J = 13 Hz), 7.25-7.65 (9 H, m), 7.85 (2 H, m), 8.40 (1 H, s); ^{13}C NMR 126.75, 127.85, 128.57, 128.69, 128.72, 131.11, 136.13, 136.19, 141.79, 161.30.

1,4-Di(4-chlorophenyl)-2-azabutadiene (**7.17b**). Recrystallized from acetone-ethyl acetate. ^{1}H NMR 6.93 (1 H, d, J = 14 Hz), 7.35 (2 H, m), 7.50 (4 H, m), 7.68 (1 H, d, J = 14 Hz), 7.85 (2 H, d, J = 8.5 Hz), 8.42 (1 H, s); ^{13}C NMR 126.32, 126.90, 126.94, 127.08, 127.19, 127.78, 128.00, 132,96, 132.01, 140.58, 158.70.

1,4-Di(4-fluorophenyl)-2-azabutadiene (**7.17c**). Recrystallized from ethyl acetate. ^{1}H NMR 6.90-7.20 (5 H, m), 7.35-7.55 (3 H, m), 7.75-7.90 (2 H, m), 8.25 (1 H, s); ^{13}C NMR 115.52, 115.64, 115.73, 115.80, 116.02, 128.17, 128.27, 129.88, 129.97, 130.28, 130.36, 130.46, 132.22, 132.26, 132.39, 132.43, 141.27, 159.63, 160.74, 162.81, 164.03, 166.161.

1,4-Di(4-methoxylphenyl)-2-azabutadiene (**7.17d**). Recrystallized from hexane-ethyl acetate. ^{1}H NMR 3.80 (3 H, s), 3.85 (3 H, s), 6.85-7.0 (5 H, m), 7.38-7.48 (3 H, m), 7.75 (2 H, d, J = 9.5 Hz), 8.25 (1 H, s); ^{13}C NMR 55.26, 55.34, 114.13, 114.24, 127.81, 129.10, 129.22, 129.40, 130.07, 140.40, 159.23, 159.70, 161.87.

1,8-Diphenyl-4-azaoctatetrene (**7.19**). Recrystallized from hexane-ethyl acetate. ^{1}H NMR 6.75-7.65 (16 H, m), 8.05 (1 H, m); ^{13}C NMR 126.42, 127.00, 127.38, 128.00, 128.51, 128.62, 128.85, 129.35, 131.77, 134.13, 135.87, 137.25, 142.76, 145.73, 161.96.

7.3.3 Representative Procedure for the Preparation of 1,3-Monoazabisylide **7.22** and Its Application to the Preparation of 2-(*3H*)-Benzazepine (**7.24**) and 2,3-Diarylpyrroles **7.27**

2-(*3H*)-Benzazepine (**7.24**). Butyllithium (3.5 ml, 8.75 mmol, 2.5 M solution in hexane) was added to a suspension of methyl triphenylphosphonium bromide (3.0 g, 8.4 mmol) in THF (40 ml) under argon at -78°C and the mixture stirred for 2 hrs at the same temperature. The yellow solution was stirred with betmip (3.5 g, 8.75 mmol) overnight at room temperature. Butyllithium (3.5 ml, 8.75 mmol, 2.5 M solution in hexane) was added to the suspension at -78°C and the mixture was stirred for 2 hrs followed by 0.5 hr at room temperature. This was stirred with phthalic dicarboxaldehyde (1.1 g, 7.5 mmol) overnight at room temperature, quenched with water (40 ml) and extracted with diethyl ether (3 x 40 ml). The organic layer was washed with 3 N NaOH (2 x 30 ml), dried ($MgSO_4$) and the solvent removed. 2-(*3H*)-Benzazepine (**7.24**) was obtained by chromatography (silica gel - diethyl ether) (0.66 g, 62%). The analysis sample was distilled (87 - 90°C / 0.5 mmHg). ^{1}H NMR 3.67 (2 H, d, J = 6 Hz), 5.95 (1 H, m), 6.65 (1 H, d, J = 10 Hz), 7.20-7.40 (4 H, m), 8.27

(1 H, s); ^{13}C NMR 48.38, 126.21, 128.96, 129.15, 129.20, 130.13, 131.87, 135.02, 137.42, 162.06.

2,3-Diphenylpyrrole (**7.27a**). Isolated by chromatography (silica gel - diethyl ether-hexane (1:2)) The analysis sample was recrystallized from ethyl acetate. ^{1}H NMR 6.40 (1 H, m), 6.82 (1 H, m), 7.20-7.40 (10 H, m), 8.15 (1 H, b); ^{13}C NMR 110.95, 118.08, 121.89, 125.66, 126.75, 127.47, 128.20, 128.24, 128.40, 128.60, 133.28, 136.57.

2,3-Di(4-methylphenyl)pyrrole (**7.27b**). Isolated by chromatography (silica gel - diethyl ether-hexane (1:1)). The analysis sample was recrystallized from hexane. ^{1}H NMR 2.35 (6 H, s), 6.37 (1 H, m), 7.30 (1 H, m), 7.05-7.35 (8 H, m), 8.10 (1 H, b); ^{13}C NMR 21.09, 21.15, 110.83, 117.68, 121.43, 127.35, 128.10, 128.38, 128.94, 129.20, 130.55, 133.74, 135.06, 136.38.

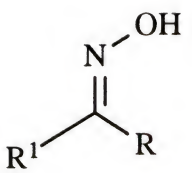
2,3-Di(pyrid-2-yl)pyrrole (**7.27c**). Isolated by chromatography (silica gel-diethyl ether-hexane (1:1)) and purified by acid-extraction as described in the procedure for isoquinoline. ^{1}H NMR 6.25 (1 H, m), 6.50 (1 H, m), 6.85 (1 H, m), 6.95 (1 H, m), 7.15 (1 H, m), 7.45 (2 H, m), 7.62 (2 H, m), 8.45 (1 H, m), 8.65 (1 H, m), 11.10 (1 H, m); ^{13}C NMR 111.97, 119.44, 120.76, 120.91 (two signals overlap), 123.44, 123.92, 128.09, 136.00, 136.06, 148.31, 149.10, 150.50, 156.05.

CHAPTER VIII
A NOVEL ADDITION-REARRANGEMENT OF O-(1-BENZOTRIAZOLYLALKYL)OXIMES WITH ORGANOLITHIUM REAGENTS. CONVENIENT NON-OXIDATIVE CONVERSION OF ALDEHYDES TO AMIDES

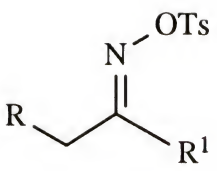
8.1 Introduction

There are several well-known rearrangements of oxime derivatives, some of which constitute satisfactory syntheses. The Beckmann reaction [60OR1] in which an oxime **8.1**, on successive treatment with an acid and water, gives a secondary amide is well known. In the Neber rearrangement, an oxime arylsulfonate **8.2** is treated with base followed by acid hydrolysis to give an α-aminoketone [64CR81]. The mechanisms of both rearrangements have been thoroughly studied and the leaving group OH_2 or OTs is considered to play a critical role. The substitution of the OH_2 by the migrating group to form an intermediate nitrilium salt in the Beckmann rearrangement, and the loss of the OTs group to form a nitrene in the Neber rearrangement, are the key steps. Few examples of oxime derivatives where a leaving group is at another position in the molecule have been reported.

In this laboratory, benzotriazole has been widely exploited as a synthetic auxiliary [91T2683]. The syntheses of Mannich-type derivatives **8.3**, **8.4** and 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (betmip, **8.7**) were achieved in excellent yields. The benzotriazole group in **8.3**, **8.4** and betmip **8.7** can be displaced easily either by reduction with hydride, or by reaction with organolithiums, Grignard reagents or zinc reagents (RLi, RMgBr or R_2Zn), leading to secondary or



8.1



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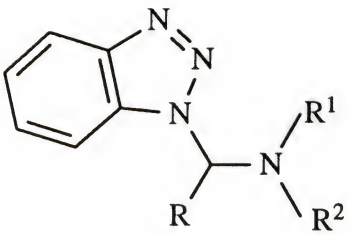

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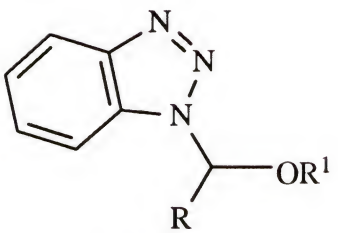

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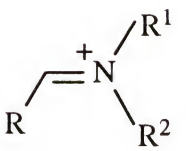

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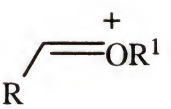

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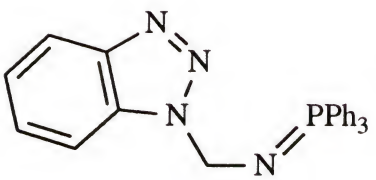

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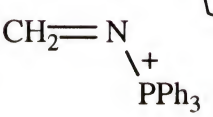

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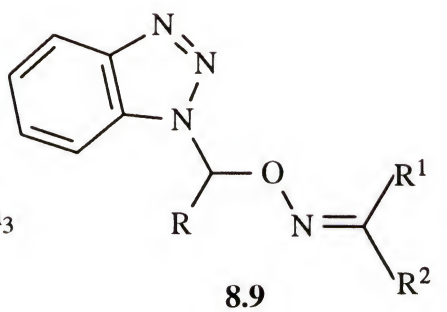


8.9

tertiary amines or ethers or primary amines in high yields. The lone pair on the exocyclic nitrogen atom in **8.3** or on the oxygen atom in **8.4** or the nitrogen anion in betmip **8.7** assists in the departure of the benzotriazole anion giving a reactive cationic intermediate **8.5**, **8.6** or **8.8**, which is susceptible to nucleophilic addition to give a variety of useful organic compounds.

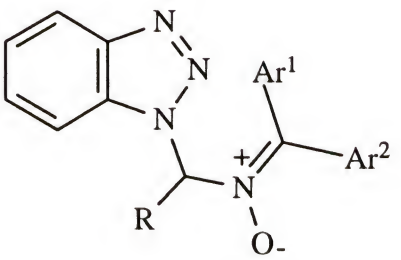
We now report new O-(1-benzotriazolyalkyl)oximes (**8.9**) and investigations of their reactions with organometallic reagents. Organolithiums in refluxing THF gave unexpected addition-rearrangements which led to N-substituted amides **8.10**. Alkyl and vinyl Grignard reagents gave alcohols **8.12a-d** as the major products with small yields of products in which the benzotriazole group of **8.9** had been displaced by the alkyl group, *e.g.* **8.11a**.

8.2 Results and Discussion

8.2.1 Preparation of O-(1-Benzotriazolylalkyl)oximes

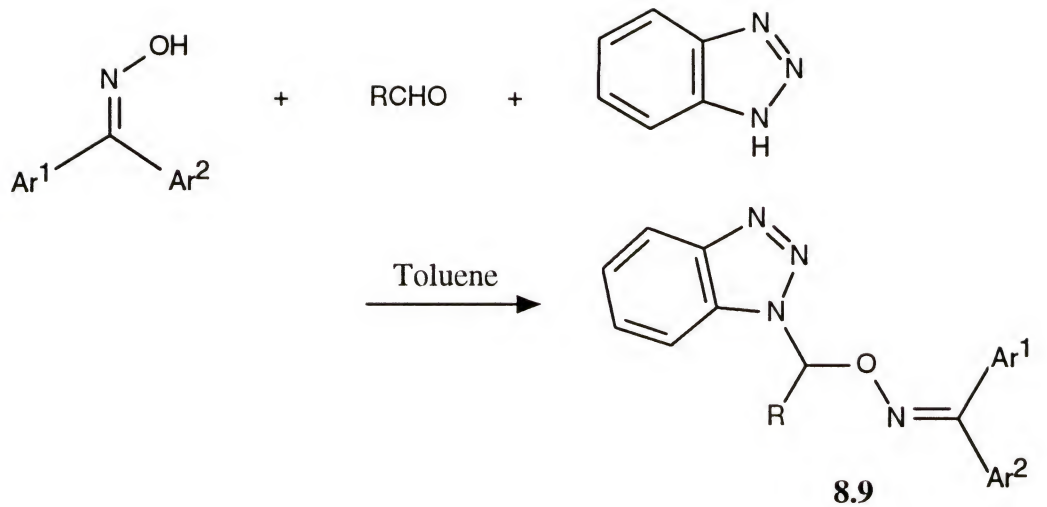
O-(1-Benzotriazolylalkyl)oximes (**8.9a-e**) were prepared in moderate to good yields by Mannich type condensation of an oxime, an aldehyde and benzotriazole in refluxing toluene containing a catalytic amount of toluenesulfonic acid. The solid O-(1-benzotriazolylalkyl)oximes (**8.9**) were easily purified by recrystallizations. Condensation of benzophenone oxime, benzotriazole and butanal or heptanal under the same conditions failed to yield the desired compounds and gave messy NMR spectra probably due to aldol condensations. Benzaldehyde was not sufficiently reactive to give the required oxime ether. Oxime derivative **8.9f** was prepared in a high yield from benzotriazol-1-ylmethyl chloride and benzophenone

oxime anion in DMSO (Scheme 8.1). The crystalline O-(1-benzotriazolylalkyl)oximes (**8.9**) were characterized by their NMR spectra and elemental analyses. The X-ray crystal structure of **8.9b** is shown in Fig. 8.1. This was determined to confirm the structure of compounds **8.9**, and particularly to exclude the possible isomeric structures **8.13.**

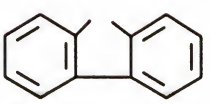


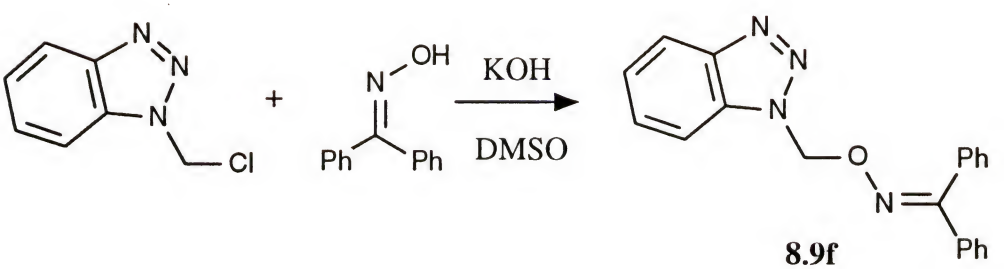
8.13

In the NMR spectra, the CH groups adjacent to the oxygen atoms displayed strongly deshielded signals (6.50-6.60 ppm for the protons and 94.8-99.8 ppm for the carbon atoms). The two CH_3 doublets in **8.9b** appeared at 0.74 ppm and 1.17 ppm. This unusually big separation could be rationalized from Fig 8.1. One CH_3 group is deshielded by the benzotriazole-ring; the steric hindrance from the two phenyl rings and the benzotriazole group prevent rotation of the isopropyl group. The characteristic C=N signals in the ^{13}C NMR spectra were at 154-160 ppm. The ^{13}C NMR signals of the two phenyl groups in each of the O-(1-benzotriazolylalkyl)oximes (**8.9**) are different. Again, one ring is clearly more deshielded by the benzotriazole group than the other. Some of the signals of the aliphatic carbons, for example in **8.9c,** are also doubled.



8.9

Compd	Ar^1	Ar^2	R
8.9a	Ph	Ph	*c* - C_6H_{11}
8.9b	Ph	Ph	*i* - Pr
8.9c	Ph	Ph	*1* - Ethylphenyl
8.9d	Ph	Ph	*t* - Bu
8.9e			*c* - C_6H_{11}



8.9f

Scheme 8.1

Table 8.1 The Preparation of O-(1-Benzotriazolylalkyl)oximes (**8.9**)

No	Yield (%)	m.p. (°C)	Recrystallization solvent
8.9a	65	164.5-165.5	Ethyl acetate
8.9b	52	139.5-140.5	Ethyl acetate
8.9c	60	81-81.5	Hexane
8.9d	45	160.0-161.0	Ethyl acetate
8.9e	55	188-187	Ethanol
8.9f	83	145.0-146.0	Ethyl acetate

Table 8.2 The Analyses of O-(1-Benzotriazolylalkyl)oximes(**8.9**)

No	Molecular Formula	C(%) Required	H(%) Required	N(%) Required	C(%) Found	H(%) Found	N(%) Found
8.9a	$C_{26}H_{26}N_4O$	76.07	6.38	13.65	76.08	6.34	13.71
8.9b	$C_{23}H_{22}N_4O$	74.57	5.99	15.12	74.22	5.97	14.74
8.9c	$C_{28}H_{30}N_4O$	76.03	7.09	13.13	75.80	7.13	12.92
8.9d	$C_{24}H_{24}N_4O$	74.97	6.29	14.69	74.65	6.25	14.69
8.9e	$C_{26}H_{24}N_4O$	76.45	5.92	13.72	76.38	5.92	13.77
8.9f	$C_{20}H_{16}N_4O$	73.15	4.91	17.06	72.97	4.91	17.19

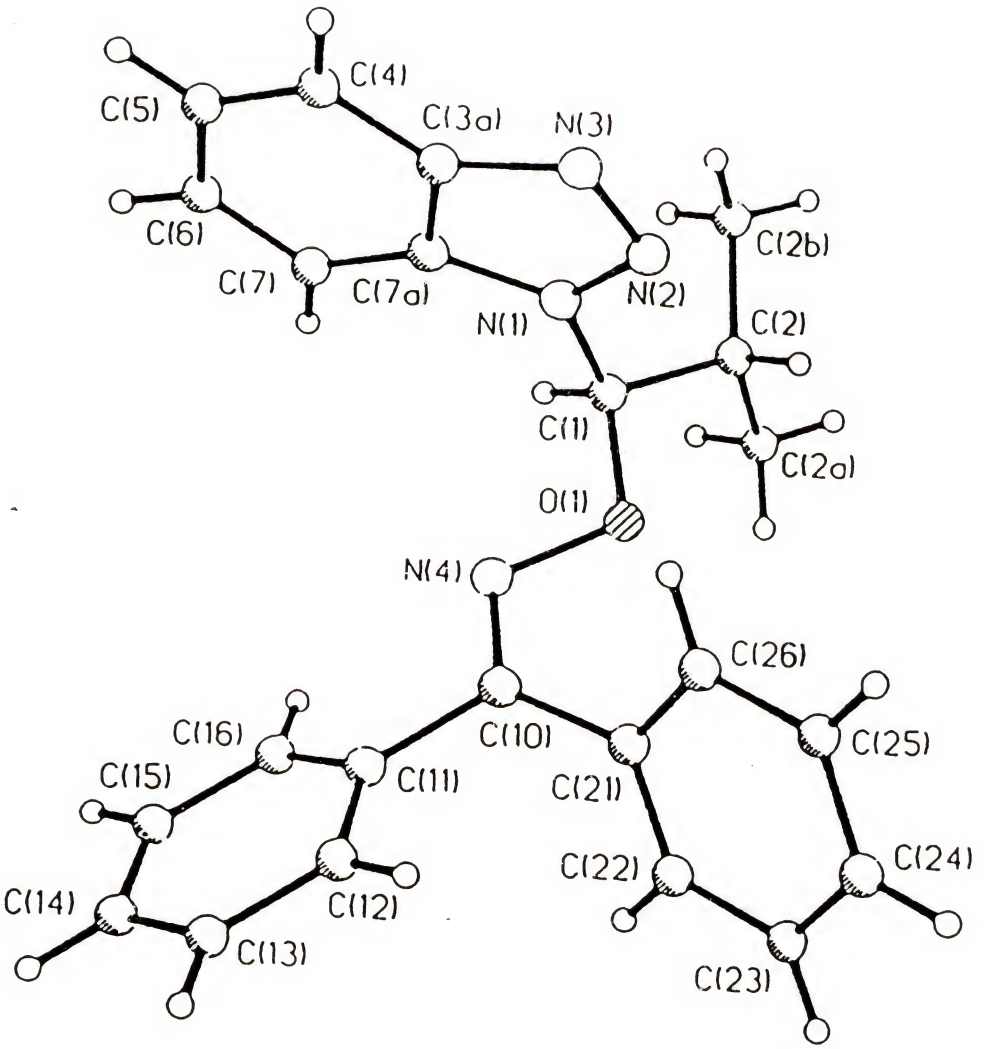
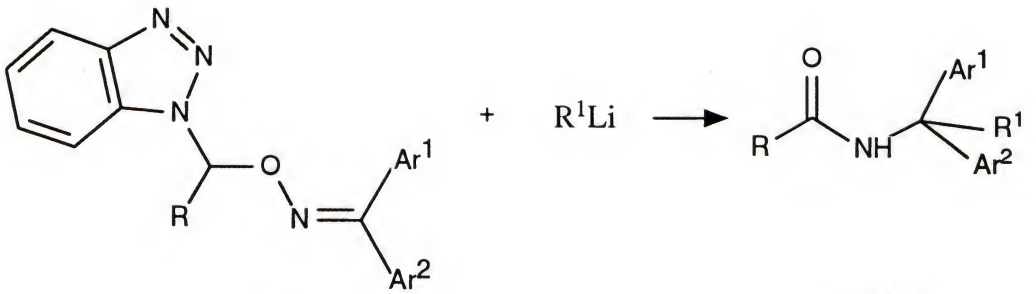


Fig. 8.1 Perspective View and Atom Labelling of the X-Ray Structure of **8.9b**

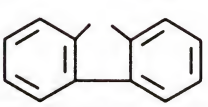
8.2.2 Reactions of O-(1-Benzotriazolylalkyl)oximes (**8.9**) with Organolithium Reagents

The reactions of O-(1-benzotriazolylalkyl)oximes (**8.9**) with organolithium reagents were carried out in THF. Two equivalents of an alkyl or aryllithium were found essential for the complete transformation of O-(1-benzotriazolylalkyl)oximes (**8.9**) into amides **8.10**. The use of one equivalent of an organolithium reagent led to a 50% recovery of the starting material. The products formed depended on the R group in O-(1-benzotriazolylalkyl)oximes (**8.9**). When R was secondary (**8.9a, 8.9b, 8.9c, 8.9e**) they underwent very clean addition-rearrangements to give exclusively N-monosubstituted amides **8.10a-g**, Scheme 8.2. When R = H **8.9f**, the reaction gave the amide **8.10h** as the major product with a significant amount of a by-product of structure $Ph_2C{=}NH$ (**8.14**, benzophenone imine). It showed a strong carbon signal at 178 ppm for the imine carbon atom and a broad proton signal at 9.37 ppm for the =NH in the crude product. Benzophenone imine was prepared by a literature method [61JOC4886] and its NMR spectra showed these two characteristic signals confirming the presence of this imine as a by-product in the reaction. With a tertiary R (**8.9d**), no amide was found in the reaction mixture and the NMR spectra showed only aromatic signals and the carbon signal at 178 ppm in the ^{13}C NMR spectrum.

The structures of the new amides were assigned from the following evidence. The high resolution mass spectrum of compound **8.10a** gave a strong molecular peak for $C_{24}H_{31}NO$ of 349.2411 (required 349.2409). The base peak 222.1410 ($C_{17}H_{18}$) was formed by McLafferty rearrangement. The other two strong peaks 292.1701 ($C_{20}H_{22}N$) and 182.0962 ($C_{13}H_{12}N$) were formed by loss of the C_4H_9 fragment from the molecular ion and by further loss of a cyclohexylcarboxyl fragment. The



8.9 **8.10**

Compd	Ar^1	Ar^2	R^1	R
8.10a	Ph	Ph	Bu	*c* - C_6H_{11}
8.10b	Ph	Ph	Me	*c* - C_6H_{11}
8.10c	Ph	Ph	Bu	*i* - Pr
8.10d	Ph	Ph	Me	*i* - Pr
8.10e	Ph	Ph	Ph	*i* - Pr
8.10f	Ph	Ph	s-Bu	*i* - Pr
8.10g	Ph	Ph	Me	*3* -Heptyl
8.10h	Ph	Ph	H	H
8.10i			Bu	*c* - C_6H_{11}

Scheme 8.2

Table 8.3 The Preparation of N-Monosubstituted Amides (**8.10**)

No	Yield (%)	m.p.(°C)	Solvent for Recrystallization
8.10a	93	188.0-190.0	hexane-ethyl acetate
8.10b	95	144.0-145.5	hexane-ethyl acetate
8.10c	90	134.0-135.0	hexane-ethyl acetate
8.10d	87	148.5-149.5	hexane-ethyl acetate
8.10e	82	194.0-194.5[a]	hexane-ethyl acetate
8.10f	78	150.0-151.0	hexane-ethyl acetate
8.10g	75	71.0-74.5	hexane
8.10h	55	134.5-135.5[b]	hexane-ethyl acetate
8.10i	58	235-236	ethyl acetate

a. Lit. 192-193°C [68IJC447] ; b. Lit. 134-135°C [57JCS115] .

Table 8.4 CHN Analyses of N-Monosubstituted Amides (**8.10**)

No	Molecular Formula	C(%)	H(%) Required	N(%)	C(%)	H(%) Found	N(%)
8.10a	$C_{24}H_{31}NO$	82.48	8.94	4.01	82.09	8.86	3.83
8.10b	$C_{21}H_{25}NO$	82.04	8.20	4.56	81.68	8.29	4.48
8.10c	$C_{21}H_{27}NO$	81.51	8.79	4.53	81.41	8.89	4.43
8.10d	$C_{18}H_{21}NO$	80.86	7.92	5.24	80.76	8.09	5.18
8.10e	$C_{23}H_{23}NO$	83.85	7.04	4.25	84.23	7.08	4.08
8.10f	$C_{21}H_{27}NO$	81.51	8.79	4.53	81.29	8.79	4.36
8.10g	$C_{25}H_{35}NO$	81.69	9.04	4.33	81.57	8.71	4.39
8.10h	$C_{14}H_{13}NO$	79.59	6.20	6.63	79. 64	6.19	6.43
8.10i	$C_{24}H_{29}NO$	82.95	8.41	4.03	82.49	8.31	3.90

infrared spectrum showed a band at 3440 cm^{-1} for NH and a strong band at 1680 cm^{-1} for amide C=O. Some aspects of the NMR spectra of the amides are worthy of note. The quaternary carbons adjacent to the nitrogen atom are usually at 60-70 ppm, however, the quaternary carbon signal of the fluorene group in **8.10i** appeared at much lower field (106.5 ppm). The NH proton is at 6.10-6.60 ppm and the carbonyl carbon at 174-176 ppm. Because of the crowded structures the CH_2 protons (C-1 of the butyl group) in **8.10a**, **8.10c** and **8.10i** close to a phenyl ring are deshielded and show complex multiplets. The ^1H NMR spectrum of one of the new amide **8.10f** was carefully assigned by the spin-spin decoupling method. The two protons of the CH_2

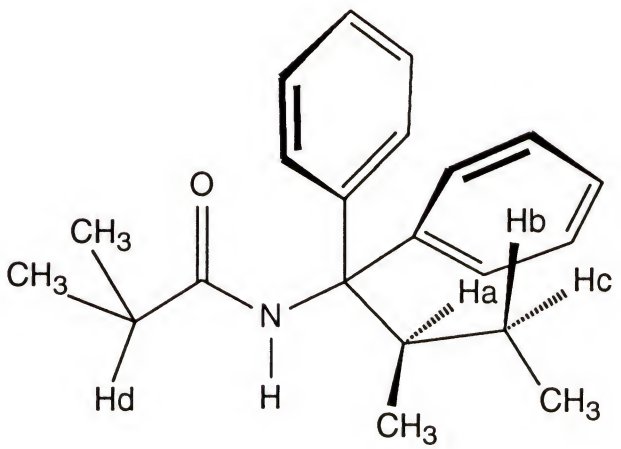


Fig 8.2 Structure of **8.10f**

group resonated separately at 0.45 ppm (H_b) and 1.65 ppm (H_c) respectively and irradiation of either of them caused the two doublets of the terminal methyl group to collapse to one doublet. H_a appeared as a one-proton multiplet at 3.30 ppm and when it was irradiated the doublet of the methyl group at 0.87 ppm collapsed to a singlet.

Even the methyls of the isopropyl group were magnetically non-equivalent and resonated as two doublets centered at 1.06 ppm. Irradiation of the heptet at 2.20 ppm caused this to collapse to two singlets at 1.02 and 1.08 ppm. The locations of H_a at an unusually low field (3.30 ppm) and of H_b at an abnormally high field (0.45 ppm) let us deduce the conformation of **8.10f** (see Fig. 8.2). This orientation of the CH and the CH_2 groups exists because the two bigger CH_3 groups rotate away from the phenyl rings. The compound also shows two distinct sets of four aromatic carbon signals.

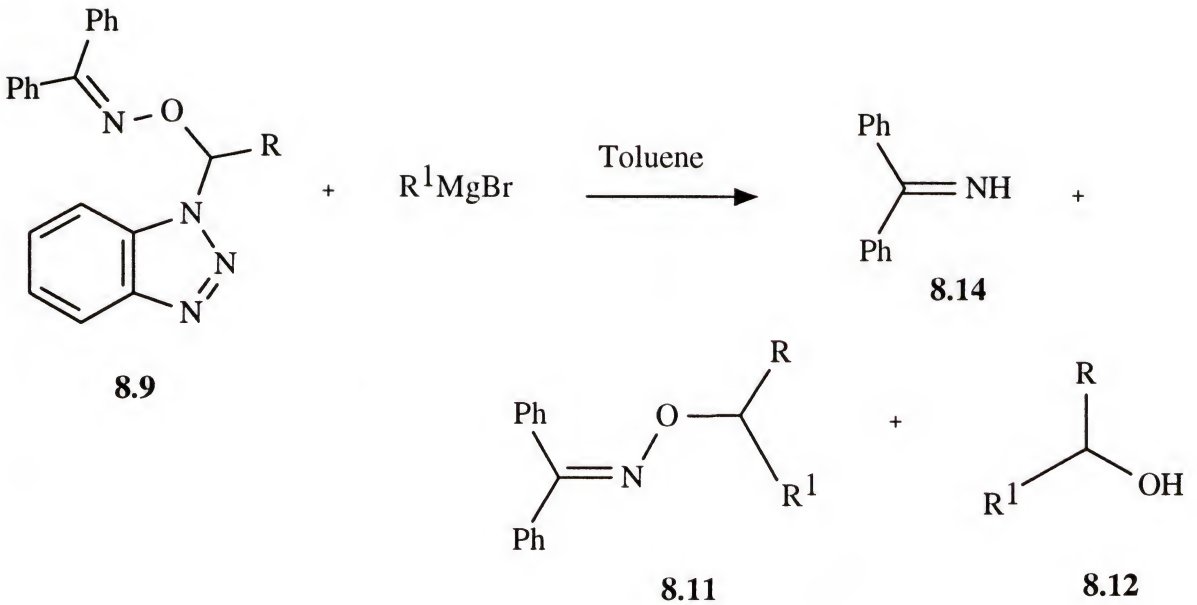
8.2.3 Grignard Reactions of O-(1-Benzotriazolylalkyl)oximes (**8.9b**)

The Grignard reactions of O-(1-benzotriazolylalkyl)oximes (**8.9**) were more complicated than expected. After attempted reactions of **8.9b** with methylmagnesium iodide or phenylmagnesium bromide in THF at room temperature or at reflux for 24 hrs the starting material was recovered unchanged. Reactions of methylmagnesium iodide with **8.9b** in refluxing toluene gave only 12% of O-alkyloxime **8.11a**, the rest of the material was probably 1,2-dimethylpropanol **8.12a** which evaporated with the toluene during work-up. After reaction of oxime **8.9a** with methylmagnesium iodide, or vinyl or propylmagnesium bromide small amounts of the O-alkyloximes **8.11b-d** could be detected in the crude NMR spectra, but the isolated products (ca.70% in each case) proved to be the alcohols (**8.12b-d**). They were identical with authentic samples prepared from cyclohexylcarboxaldehyde and the respective Grignard reagents. The proton signals and the carbon signals of the CH groups adjacent to the oxygen atoms in **8.11** and **8.12** were different. The smaller signals of **8.11** in the crude products were at 79-84 ppm in the ^{13}C NMR spectra and at about 4.10-4.30 ppm in ^{1}H NMR spectra. In contrast, the carbon signals of the alcohols **8.12** were found below 78 ppm and the

proton signals were at about 3.5 ppm. The ratios of **8.11** to **8.12** could be calculated based on the integration of these two proton signals and were about 1 to 5 in each case. The crude products also showed strong signals at ca. 178 ppm in the ^{13}C NMR spectra which were probably due to $Ph_2C{=}NH$ (**8.14**) as mentioned above. **8.9f**, derived from formaldehyde, failed to react with either methylmagnesium iodide or phenylmagnesium bromide in refluxing toluene over two days.

O-(1,2-Dimethylpropyl)benzophenone oxime (**8.11a**) obtained from the reaction of **8.9b** with methylmagnesium iodide was isolated (12%) and its structure established by the NMR data and the mass spectrum. The high resolution mass spectrum gave a strong molecular ion ($C_{18}H_{21}NO$) at 267.1623 (required 267.1622) and a signal at 155 ppm in the ^{13}C NMR spectrum is reasonable for the C=N carbon signal. The alcohols **8.12b-d** were isolated by distillation from reactions of **8.9a** with methylmagnesium iodide, and vinyl and propylmagnesium bromide, respectively. Their spectra were identical to those of the corresponding alcohols obtained from reactions of cyclohexylcarboxaldehyde with methylmagnesium iodide and vinyl-and propylmagnesium bromide [88TL3887] [90TL7115] [85CB1421].

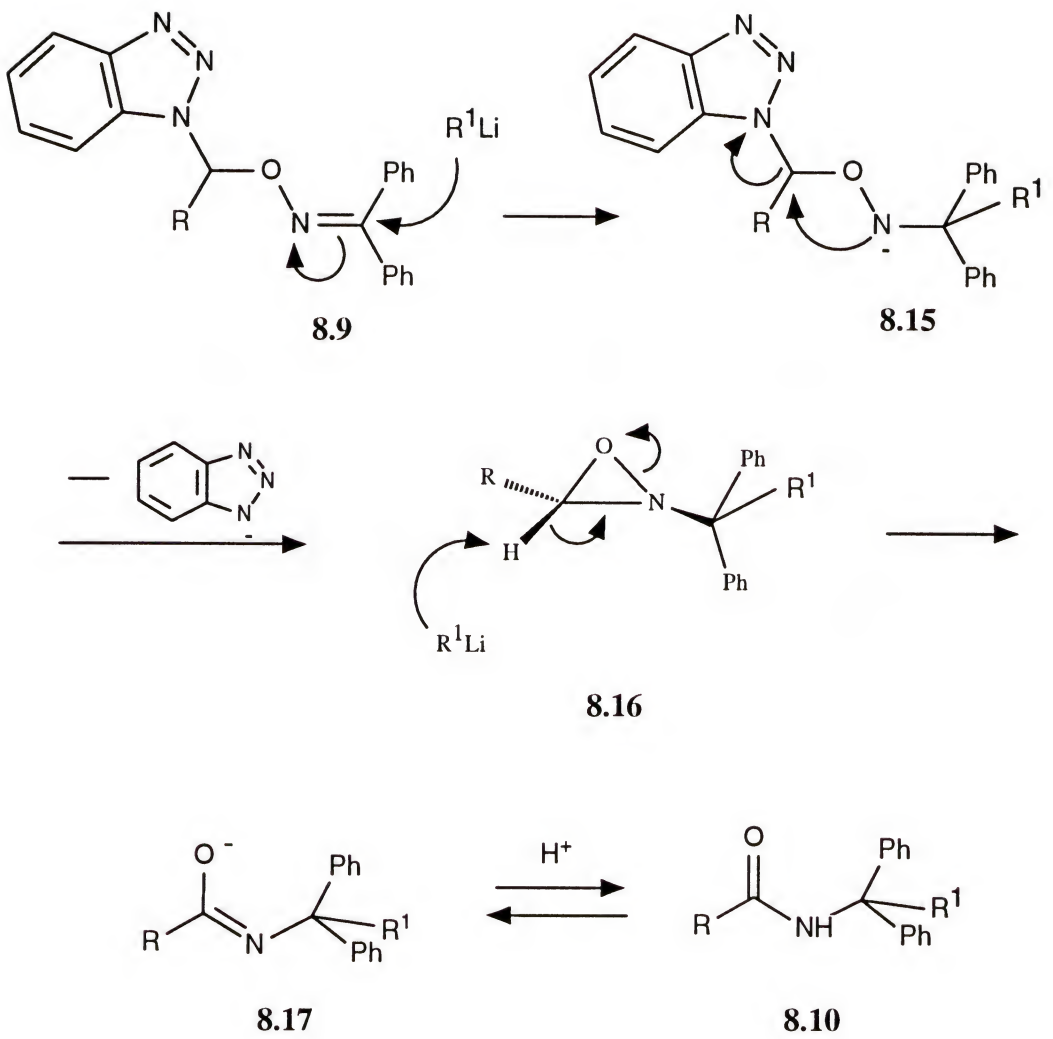
The proposed mechanism for the addition-rearrangement reaction is shown in Scheme 8.4. Nucleophilic addition of an organolithium reagent to the C=N bond gives a nitrogen anion which causes an intramolecular nucleophilic substitution to displace the benzotriazole to give an oxaziridine **8.16**. The second molecule of the organolithium reagent acts as a base to deprotonate the oxaziridine ring which opens *via* the imide **8.17** to the amide. Grignard reagents are apparently not powerful enough to attack the hindered C=N bond. Several recent papers describe the addition of organolithium reagents to oxime C=N bonds [87TL4973] [88TL3455] [91S559]. The formation of amides in the present work is facilitated by the easy displacement of the



8.9 **8.14** **8.11** **8.12**

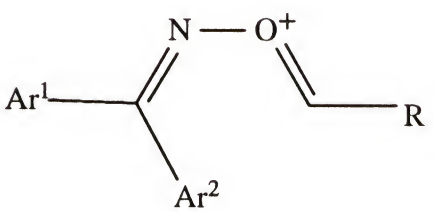
8.11, 8.12	R	R^1
a	i-Pr	Me
b	c-C_6H_{11}	Me
c	c-C_6H_{11}	Vinyl
d	c-C_6H_{11}	Pr

Scheme 8.3



Scheme 8.4 Mechanism for the Formation of Amides

benzotriazole group. The mechanism for the formation of O-alkyloximes **8.11** in Grignard reactions is probably *via* the intermediate **8.18** based on the fact that the reaction needs assistance from the isopropyl group at the carbon atom adjacent to the oxygen in **8.9b**. Easy rupture of the N-O bond (bond strength 48 kcal/mol [69JOC1430]) is the possible reason of the formation of alcohols **8.12**.



8.18

In conclusion, although Grignard reactions of O-(1-benzotriazolyalkyl)oximes (**8.9**) afforded alcohols which are better available directly from the corresponding aldehydes and Grignard reagents, a new addition-rearrangement reaction with organolithium reagents has been discovered which produces amides. This provides a mild, non-oxidative route from aldehydes to amides in which the carbon attached to the amide nitrogen is tertiary.

8.3 Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 MHz spectrometer in $CDCl_3$ using TMS as an internal reference for ^{1}H spectra and $CDCl_3$

for ^{13}C NMR spectra. Elemental analyses were performed at the University of Florida. THF and toluene were freshly distilled from sodium-benzophenone ketyl immediately before use.

8.3.1 Representative Procedure for the Preparation of O-(1-Benzotriazolylalkyl)-oximes (**8.9**)

O-(Benzotriazol-1-ylcyclohexyl)methylbenzophenone oxime (**8.9a**). A mixture of cyclohexylcarboxaldehyde (8.7 g, 77.7 mmol), benzotriazole (9.1 g, 76.5 mmol) and toluenesulfonic acid (0.5 g) was stirred overnight in toluene (150 ml). Benzophenone oxime (15 g, 76.5 mmol) in toluene (75 ml) was added and the mixture refluxed under a Dean-Stark trap for 24 hrs. The solvent was removed under vacuum and 100 ml of diethyl ether added. The mixture was refrigerated for 10 hrs and the substituted oxime collected in a 65% yield. ^{1}H NMR 1.02-1.29 (m, 6 H), 1.60-1.77 (m, 3 H), 2.03-2.38 (m, 2 H), 6.53 (d, J = 9.5 Hz, 1 H), 7.15-7.52 (m, 13 H), 8.06 (d, J = 7.0 Hz, 1H); ^{13}NMR 25.22, 25.91, 28.02, 29.03, 40.12, 96.10, 11.20, 119.77, 123.84, 127.00, 127.89, 127.95, 128.06, 128.92, 128.96, 129.76, 132.12, 132.58, 135.18, 146.31, 159.60. Other data are in Tables 8.1 and 8.2.

Similarly were prepared:

O-(1-Benzotriazol-1-yl-2-methyl)propylbenzophenone oxime (**8.9b**). ^{1}H NMR 0.74 (d, J = 6.5 Hz, 3H), 1.17 (d, J = 6.5 Hz, 3H), 2.70 (m, 1H), 6.45 (d, J = 9.0 Hz, 1H), 7.16-7.50 (m, 13H), 8.05 (d, J = 7.0 Hz, 1H); ^{13}C NMR 18.04, 18.82, 31.50, 97.04, 111.20, 119.79, 123,85, 127.03, 127.89, 127.95, 128.08, 128.89, 128.97, 129.80, 132.02, 132.56, 135.11, 146.32, 159.65.

O-(1-Benzotriazol-1-yl-2-ethyl)hexylbenzophenone oxime (**8.9c**). ^{1}H NMR 0.72 (m, 3 H), 0.85-1.35 (m, 9 H), 1.62 (m, 2 H), 2.42 (m, 1 H), 6.65 (dd, 1 H),

7.20-7.50 (m, 13 H), 8.08 (m, 1 H); ^{13}C NMR 9.93, 9.97, 13.69, 13.91, 21.46, 21.51, 22.50, 22.89, 27.60, 27.89, 28.15, 41.36, 41.43, 94.73, 94.83, 111.20, 111.26, 119.74, 123.96, 125.55, 127.10, 128.08, 128.00, 128.78, 128.00, 128.94, 129.80, 132.16, 132.22, 132.65, 135.02, 135.05, 146.20, 159.74.

O-(1-Benzotriazol-1-yl-2,2-dimethyl)propylbenzophenone oxime (**8.9d**). ^{1}H NMR 1.03 (s, 9 H), 6.60 (s, 1 H), 7.15-7.40 (m, 10 H), 7.50 (m, 3 H), 8.03 (m, 1 H); ^{13}C NMR 26.04, 37.33, 99.80, 112.32, 119.48, 123.55, 126.85, 127.89, 127.97, 128.09, 129.04, 129.18, 129.87, 132.56, 132.69, 134.87, 145.84, 159.97.

O-(Benzotriazol-1-ylcyclohexyl)methylfluorenone oxime (**8.9e**). H^{1} NMR 1.20 (m, 4 H), 1.40 (m, 2 H), 1.70 (m, 2 H), 1.85 (m, 1 H), 2.35 (m, 1 H) 2.85 (m, 1 H). 6.60 (d, 1 H, J = 9.5 Hz), 7.05-7.55 (m, 11 H), 7.85 (d, 1 H, J = 7.5 Hz), 8.05 (d, 1 H, J = 7.0 Hz), 8.35 (d, 1 H, J = 7.0 Hz); ^{13}C NMR 25.17, 25.27, 25.88, 28.10, 29.33, 40.05, 95.35, 110.76, 119.68, 119.84, 119.90, 121.84, 123.92, 127.39, 127.77, 128.22, 129.16, 129.99, 130.28, 131.43, 132.56, 134.64, 140.18, 141.65, 146.19, 154.00.

O-(Benzotriazol-1-ylmethyl)benzophenone oxime (**8.9f**). A mixture of benzophenone oxime (10.0 g, 51 mmol) in DMSO (100 ml) and NaOH (4.0 g, 100 mmol) in water (50 ml) was heated in an oil bath maintained at 60^{o}C for 30 min. Benzotriazolylmethyl chloride (8.5 g, 51 mmol) in DMSO (20 ml) was added and stirring continued at 60^{o}C for 5 hrs. The mixture was poured onto ice and the product collected and recrystallized (ethanol-ethyl acetate) to a white solid (85%). ^{1}H NMR 6.5 (s, 2 H), 7.05-7.55 (m, 12 H), 7.80 (d, 1H, J = 9.0 Hz), 8.06 (d, J = 7.0 Hz, 1 H); ^{13}C NMR 78.86, 127.95, 128.11, 128.22, 129.05, 129.86,132.18, 133.10, 135.14, 110.53, 119.70, 124.07, 127.61, 132.18, 146.11, 159.88.

8.3.3 Representative Procedure for the Preparation of N-Monosubstituted Amides (**8.10**)

N-(1,1-Diphenylpentyl)cyclohexylcarboxamide (**8.10a**). Butyl lithium (2.5 M, 4.5 ml, 11.2 mmol) was added to a solution of O-(1-benzotriazol-1-yl-1-cyclohexyl)methylbenzophenone oxime (**8.9a**) (2.0 g, 4.90 mmol) in THF (80 ml) over 2 min under argon at -78^{o}C. The solution was stirred, allowed to warm to room temperature over ca. 2 hrs and refluxed for 2 hrs. The product was quenched with water (30 ml) and diluted with diethyl ether (80 ml). The organic layer was washed with 3 N NaOH (30 ml x 2), dried ($MgSO_4$) and the solvent removed to give the amide. ^{1}H NMR 0.83 (t, J = 7.0 Hz, 3 H), 1.10- 1.90 (m, 14 H), 2.15 (m, 1 H), 2.63 (m, 2 H), 6.20 (s, 1 H), 7.15-7.35 (m, 10 H); ^{13}C NMR 14.08, 22.82, 25.70, 26.48, 29.76, 37.07, 46.25, 64.30, 126.34, 126.53, 128.10, 145.63, 174.62. Other data are in the Tables 8.3 and 8.4.

N-(1,1-Diphenylethyl)cyclohexylcarboxamide (**8.10b**). ^{1}H NMR 1.15-2.15 (m, 11 H), 2.20 (s, 3 H), 6.13 (s, 1 H), 7.15-7.35 (m, 10 H); ^{13}C NMR 25.58, 29.58, 27.36, 45.94, 61.73, 126.26, 126.77, 128.17, 146.17, 174.74.

N-(1,1-Diphenylpentyl)isobutyramide (**8.10c**). 1H NMR 0.83 (t, J = 7.0 Hz, 3 H), 1.08-1.22 (m, 8 H), 1.32 (m, 2 H), 2.41 (m, 1 H), 2.65 (m, 2 H), 6.12 (s, 1 H), 7.15-7.35 (m, 10 H); ^{13}C NMR 14.08, 19.63, 22.83, 26.49, 36.37, 37.15, 64.35, 126.36, 126.57, 128.11, 145.59, 175.45.

N-(1,1-Diphenylethyl)isobutyramide (**8.10d**). ^{1}H NMR 1.15 (d, J = 7.0 Hz, 6 H), 2.21 (s, 3 H), 2.37 (m, 1 H), 6.12 (s, 1 H), 7.20-7.35 (m, 10 H); ^{13}C NMR 19.65, 27.44, 36.30, 61.96, 126.39, 128,98, 128.36, 146.30, 175.35.

N-(Triphenylmethyl)isobutyramide (**8.10e**). ^{1}H NMR 1.13 (m, 6 H), 2.42 (m, 1 H), 6.57 (s, 1 H), 7.13-7.45 (m, 15 H); ^{13}C NMR 19.52, 36.45, 69.96, 69.99,

126.88, 127.85, 128.56, 144.82, 175.38.

N-(1,1-Diphenyl-2-methylbutyl)isobutyramide (**8.10f**). ^{1}H NMR 0.45 (m, 1 H), 0.87 (d, J = 7.0 Hz, 3 H), 0.95 (dd, J = 7.0 Hz, 3 H), 1.06 (dd, J = 7.0 Hz, 6 H), 1.65 (m, 1 H), 2.20 (m, 1 H), 3.30 (m, 1 H), 6.08 (s, 1 H), 7.20-7.40 (m, 10 H); ^{13}C NMR 12.40, 14.48, 19.40, 19.42, 25.68, 36.40, 38.61, 68.54, 126.68, 126.78, 127.30, 127.36, 128.45, 128.50, 142.65, 143.40, 175.14.

N-(1,1-Diphenylethyl)-1-ethylhexanamide (**8.10g**). ^{1}H NMR 0.78-1.60 (m, 20 H), 1.98 (m, 1 H), 2.65 (m, 2 H), 6.10 (s, 1 H), 7.15-7.35 (M, 10 H); ^{13}C NMR 12.15, 13.94, 14.00, 22.75, 22.94, 26.16, 26.51, 29.81, 32.62, 37.31, 50.40, 64.75, 126.59, 126.69, 127.96, 145.57, 145.61, 174.62.

N-(Diphenylmethyl)formamide (**8.10h**). ^{1}H NMR 6.23 (d, J = 8.5, 1 H), 6.85 (b, 1 H), 7.15-7.40 (m, 10 H), 8.10 (s, 1 H); ^{13}C NMR 55.57, 127.28, 127.46, 128.57, 140.83, 160.37.

N-(9-Butylfluoren-9-yl)cyclohexylcarboxamide (**8.10i**). ^{1}H NMR 0.70-1.85 (m, 18 H), 2.0 (m, 1 H), 2.35 (m, 2 H), 5.85 (s, 1 H), 7.25-7.40 (m, 4 H), 7.50-7.75 (m, 4 H); ^{13}C NMR 13.8, 22.68, 25.65, 29.64, 37.81, 45.80, 66.82, 106.50, 119.82, 123.35, 127.71, 128.22, 140.02, 148.10,175.45.

8.3.3 Representative Procedure for the Grignard Reactions of **8.9**

O-(1,2-Dimethylpropyl)benzophenone oxime (**8.11a**). CH_3MgI (16.5 mmol) in diethyl ether (40 ml) was dropped into a solution of O-(1-benzotriazol-1-yl-2-methyl-propyl)benzophenone oxime (1.5 g, 4 mmol) in toluene (60 ml) at room temperature. After most of diethyl ether was removed by distillation on an oil bath ($80^{o}C$), the solution was refluxed overnight. The product was quenched with water (10 ml) and extracted with diethyl ether (40 ml x 2). The organic layer was washed with 3 N

NaOH (2 x 20 ml), dried ($MgSO_4$), the solvent removed and the residue purified *via* a silica gel column eluted with chloroform to give O-(1,2-dimethylpropyl)benzophenone oxime as an oil (0.13 g, 12%). HRMS 267.1622, required 267.1623. ^1H NMR 0.87 (dd, 6 H), 1.21 (d, J = 6.5 Hz, 3 H), 1.90 (m, 1 H), 4.13 (m, 1 H), 7.18-1.18 (m, 10 H); ^{13}C NMR 16.81, 16.61, 18.59, 32.20, 84.52, 127.76, 128.07, 128.21, 128.38, 128.81, 129.40, 133.68, 137.07, 155.42.

1-Cyclohexylethanol (**8.12a**). Obtained from the reaction of **8.9a** with methylmagnesium iodide in 75% yield. Purified by distillation (b.p. 71-74 ^oC/5mmHg). ^1H NMR 0.90-1.35, 1.62-1.92 (m, 14 H), 2.30 (bs, 1 H), 3.55 (m, 1 H); ^{13}C NMR 20.28, 26.53, 26.24, 26.16, 28.66, 28.45, 45.11, 72.05.

1-Cyclohexylallyl alcohol (**8.12b**). Obtained from the reaction of **8.9a** with vinylmagnesium bromide in 70% yield. Purified by distillation (b.p. 73-76^oC/3mmHg). ^1H NMR 0.85-1.95 (m, 6 H), 2.05-1.90 (m, 5 H), 2.05 (bs, 1 H), 3.82 (dd, 1 H), 5.15 (m, 2 H), 5.85 (m, 1 H); ^{13}C NMR 26.00, 26.05, 26.43, 28.30, 28.63, 43.35, 77.60, 115.27, 139.75.

1-Cyclohexylbutan-1-ol (**8.12c**). Obtained from the reaction of **8.9a** with propylmagnesium bromide in 70% yield (b.p. 79-82^oC/3mmHg). ^1H NMR 0.88 (t, J = 7.0 Hz, 3 H), 0.90-1.85 (m, 15 H), 3.0 (bs, 1 H), 3.35 (m, 1 H); ^{13}C NMR 13.98, 18.98, 26.11, 26.26, 26.44, 27.65, 29.11, 36.13, 43.48, 75.68.

Benzophenone imine (**8.14**). Obtained in the reaction of **8.9a** with propylmagnesium bromide in 60% yield. Purified by distillation (b.p. 130-132^oC/1mmHg, lit. b.p. 137^oC/0.5mmHg [61JOC4886]). Repeating the literature preparation [61JOC4886] gave a product (65% yield) with the identical spectra. ^1H NMR 7.25- 7.80 (m, 5 H), 9.37 (b, 1 H); ^{13}C NMR 127.71, 127.80, 129.28, 138.70, 177.70.

8.3.4 X-ray Crystal Structure Determination (determined by Dr. Peter J. Steel)

Crystal Data - $C_{23}H_{22}N_4O$, FW = 370.4. Orthorhombic, a = 20.718(14), b = 63.84(4), c = 5.935(5) Å, V = 7898(9) $Å^3$ (by least-squares refinement on 25 accurately centered reflections with $2\Theta>13^o$, λ = 0.7107 Å) at - 80°C. Space group $Fdd2$, Z = 16, D_X = 1.246 g cm^{-3}. Crystal dimensions 0.60 x 0.16 x 0.04 mm, μ (M_o - K_α) = 0.74 cm^{-1}, F(000)=3136.

Data Collection and Processing [92AC(C)48]- Nicolet R3m four- circle diffractometer, $\omega/2\Theta$ scan mode ($1.5\theta \leq 28^o$, +h,k,l), graphite-monochromated Mo- Kα radiation; 2006 unique reflections measured at - 80°C, giving 806 with $I > 2.5\sigma(I)$. No absorption correction or crystal decay. Structure Solution and Refinement (Full tables of atom coordinates, bond lengths and angles, anisotopic displacement parameters and calculated hydrogen atom coordinates have been deposited at the Cambrige Crystallographic Data Center) - Direct methods gave all non-hydrogen atoms. Full-matrix least-squared refinment with all non-hydrogen atoms anisotropic and hydrogens in calculated positions with isotropic temperature factors. The function minimized was $\Sigma w (|F_O| - |F_C|)^2$, with $w = [\sigma^2(F_o) + 0.0005F_o^2]^{-1}$. Final R and R_w values are 0.051 and 0.048 with S = 1.06. Final difference map features < *0.26* e $Å^{-3}$ Y For programs and computers see reference [92AC(C48)325] . There are no unusual features in the bonding geometry or molecular packing

Table 8 .5 Bond Angles(°).

N(2)-N(1)-C(7A)	110.3(8)	N(2)-N(1)-C(1)	120.1(8)
C(7A)-N(1)-C(1)	129.3(8)	N(1)-N(2)-N(3)	108.8(9)
N(2)-N(3)-C(3A)	108.0(11)	N(3)-C(3A)-C(4)	131.2(12)
N(3)-C(3A)-C(7A)	108.8(10)	C(4)-C(3A)-C(7A)	119.9(11)
C(3A)-C(4)-C(5)	118.4(12)	C(4)-C(5)-C(6)	121.5(10)
C(5)-C(6)-C(7)	121.5(12)	C(6)-C(7)-C(7A)	116.6(12)
N(1)-C(7A)-C(3A)	104.0(10)	N(1)-C(7A)-C(7)	133.8(11)
C(3A)-C(7A)-C(7)	122.1(10)	N(1)-C(1)-C(2)	112.7(8)
N(1)-C(1)-O(1)	108.1(9)	C(2)-C(1)-O(1)	106.8(7)
C(1)-C(2)-C(2A)	109.3(9)	C(1)-C(2)-C(2B)	111.3(7)
C(2A)-C(2)-C(2B)	109.1(9)	C(1)-O(1)-N(4)	107.7(7)
O(1)-N(4)-C(10)	109.2(9)	N(4)-C(10)-C(11)	114.6(10)
N(4)-C(10)-C(21)	126.7(9)	C(11)-C(10)-C(21)	118.7(9)
C(10)-C(11)-C(12)	118.8(11)	C(10)-C(11)-C(16)	121.4(10)
C(12)-C(11)-C(16)	119.8(9)	C(11)-C(12)-C(13)	119.3(12)
C(12)-C(13)-C(14)	119.6(11)	C(13)-C(14)-C(15)	120.6(10)
C(14)-C(15)-C(16)	119.5(12)	C(11)-C(16)-C(15)	121.0(11)
C(10)-C(21)-C(22)	118.3(10)	C(10)-C(21)-C(26)	119.9(8)
C(22)-C(21)-C(26)	121.7(10)	C(21)-C(22)-C(23)	119.3(11)
C(22)-C(23)-C(24)	120.0(9)	C(23)-C(24)-C(25)	121.0(11)
C(24)-C(25)-C(26)	119.3(12)	C(21)-C(26)-C(25)	118.5(9)

Table 8 .6 Bond Lengths(Å)

N(1)-N(2)	1.357(11)	N(1)-C(7A)	1.370(13)
N(1)-C(1)	1.488(12)	N(2)-N(3)	1.310(14)
N(3)-C(3A)	1.385(16)	C(3A)-C(4)	1.399(14)
C(3A)-C(7A)	1.390(19)	C(4)-C(5)	1.355(18)
C(5)-C(6)	1.400(21)	C(6)-C(7)	1.381(15)
C(7)-C(7A)	1.394(18)	C(1)-C(2)	1.502(13)
C(1)-O(1)	1.449(11)	C(2)-C(2A)	1.564(16)
C(2)-C(2B)	1.561(13)	O(1)-N(4)	1.435(11)
N(4)-C(10)	1.292(14)	C(10)-C(11)	1.523(14)
C(10)-C(21)	1.501(16)	C(11)-C(12)	1.408(16)
C(11)-C(16)	1.383(18)	C(12)-C(13)	1.409(15)
C(13)-C(14)	1.409(20)	C(14)-C(15)	1.375(17)
C(15)-C(16)	1.406(15)	C(21)-C(22)	1.393(12)
C(21)-C(26)	1.386(17)	C(22)-C(23)	1.401(16)
C(23)-C(24)	1.374(18)	C(24)-C(25)	1.403(14)
C(25)-C(26)	1.421(16)		

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The reference system used here is that from the book series "Comprehensive Heterocyclic Chemistry", edited by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984. Throughout this dissertation, references are designed a number-letter coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted. Some commonly used additional notes are given below:

1. The list of the reference is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.

2. In the reference list, the code is followed by the complete literature citation in the convenient manner.

3. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.

4. Journal volume number are not included in the code numbers unless more the one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.

5. Patents are assigned appropriate three letter codes.

6. Frequently cited books are assigned codes, but the whole code is now

prefixed by the letter "B".

7. Less common journal and books are given the code "MI" for miscellaneous.

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BIOGRAPHICAL SKETCH

Jinlong Jiang was born in March 1962 in Chunan, Zhejiang Province, the Peoples Republic of China. He received a Master of Science Degree in organic chemistry from the Department of Chemistry at Hangzhou University in July 1985. From September 1985 to July 1988, he worked at Hangzhou University as a faculty member.

In July 1988, he joined the research group of Professor Alan R. Katritzky as a research assistant in Gainesville. In January 1990, he started the Ph.D. Program in the Chemistry Department at the University of Florida.

He is married and has a two year old daughter, Eileen, who was born in Gainesville.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of the Doctor of Philosophy.

Alan R. Katritzky, Chair
Kenan Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of the Doctor of Philosophy.

William Jones
Distinguished Service Professor
of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of the Doctor of Philosophy.

Kirk Schanze
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of the Doctor of Philosophy.

John Eyler
Professor of Chemistry

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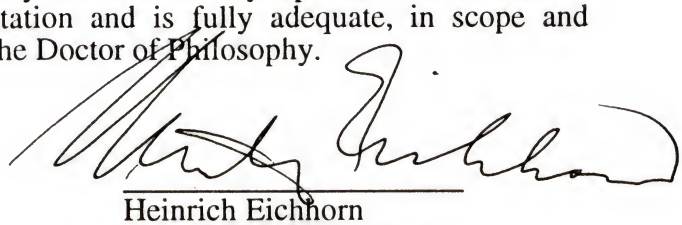

Heinrich Eichhorn
Professor of Astronomy

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor Philosophy.

May, 1993

Dean, Graduate School